American Heart Journal

February, 1961, Volume 61, Number 2

Editorial

Considerations on the evolution of heart diseases in Algeria

Ch. Sarrouy, M.D.
L. Sendra, M.D.
G. Duboucher, M.D.
Algiers, Algeria

Algeria is certainly nowadays one of the countries which provide the best opportunities for the study of geographic pathology. Its contrasting populations, one entirely European and subject to the advantages and stresses of modern life, the other a rural aggregate with very low standards of life, have for a long time presented two very different aspects of pathology. However, those differences, which were especially marked in the cardiovascular field, are undergoing at the present time profound modifications, the causes of which in some instances may be easily grasped, i.e., the extension of public health, the accelerated "occidentalization" of the urban population, and the transplantation of rural Mussulmans to metropolitan France. Thus, certain factors, such as diet, demography, the strain of city life, lend themselves to analysis in a truly "experimental" manner.

In general, in Algeria at the present time, the acquired cardiovascular diseases are on the decrease, whereas other types are on the increase.

The types of heart disease which are declining in incidence are those due to nutritional deficiency, parasites, and infection. It is true that nutritional deficiences have never played an outstanding role in cardiovascular disease in Algeria. The pure forms of beriberi heart disease have been almost unknown here for a long time, and, at present, avitaminosis is rarely proposed as the cause of cardiac insufficiency. Among the parasitic diseases of the heart, only the hydatid cyst is worth mentioning in this region, and cases of it are very exceptional. The incidence of direct infectious involvement of the endocardium and pericardium has undergone in North Africa the same decline as elsewhere since the use of antibiotics was begun. Bacterial endocarditis is observed only sporadically. The recent epidemic of influenza did not increase the annual number of cases of benign acute pericarditis. Tuberculosis of the pericardium is cured in a large proportion of the cases, but severe forms are still seen which, in Algeria perhaps more than elsewhere, develop readily into symphysis which requires an early pericardiectomy. Historic typhus fever has not reappeared for 17 years. The epidemic of 1940-1942 did not yield any

From the University of Algiers, Mustapha Hospital, Algiers, Algeria.
Received for publication Aug. 12, 1959.

evidence in favor of the role of *Rickettsia prowazekii* in the constitution of certain subacute endocarditides and certain instances of thromboangiitis of the Buerger type.

On the contrary, for two or three decades other forms of heart disease have been constantly increasing in incidence in Algeria. Among these are arterial hypertension, arteriosclerosis, and rheumatic heart disease. An increase in the incidence of these diseases can be explained by the fact that the present heart disease in the Mussulman population is falling more and more into line with that of the populations of European countries, whereas until World War I the Mussulman population had been almost completely exempt from these forms of heart disease.

Thus, formerly a high blood pressure in a Mussulman of North Africa was diagnostic of glomerulonephritis. Today the apparently primitive *hypertensive disease* is frequently observed among the Mussulmans who live in the towns and those who work in the capital, but is seen infrequently among the rural population. It appears to us that the agitation and overcrowding of the cities, the noise, the irregularity of work hours, and especially the night work, play a more important pathogenic role than do quantitative and qualitative changes in the diet.

What is true for arterial hypertension is also true for angina pectoris, peripheral arteritis, and, in general, all forms of atheroma. It has become a truism to say that the development of hypertension and atherosclerosis among the Mussulmans is parallel to the extension of occidental civilization.

But the pathologic evolution of rheumatic fever, which represents the most frequent cause of heart disease in Algeria, is undoubtedly the most striking. For this reason, and because of a more complete personal documentation in this than in any other area of cardiology, we will discuss this subject in more detail.

It is known that the geographic distribution of this disease has for a long time appeared to be uneven: frequent in temperate countries and rare in the hot regions of Africa, Asia, and Oceania. North Africa, which is situated at the limits of the temperate and the subtropical regions, was no exception to this rule: the incidence of rheumatic fever was much lower in this country than in metropolitan France.

In 1905, Dumolard and Lemaire[1] mentioned the extreme rarity of rheumatic fever among the natives and cited a study of Gros, who had observed only 4 or 5 cases of valvular heart disease among the 10,000 natives whom he examined. Andrieu,[2] in his thesis in 1926, reported army statistics for the 5-year period 1908-1912 which showed that the rheumatic morbidity in Algeria was 9.26 per 1,000, or less than half of the morbidity observed among the troops stationed in metropolitan France. The incidence of rheumatic fever in the European and in the Algerian native, as deduced from the figures published by Fabiani,[3] in 1932, by Aubry and Thiodet,[4] in 1937, and from data collected in the Clinique Medicale Infantile d'Alger, was as follows: 14.2 per 1,000 in the European adult, 19.3 per 1,000 in the European child of 3 to 15 years of age, 3 per 1,000 in the Mussulman adult, and 4.2 per 1,000 in the Mussulman child. In all, these works attest the rarity of rheumatic fever in the Algerian native. The role of the climate was of little importance, as evidenced by the fact that the incidence of rheumatic fever in the European living in Algeria was as high as that in metropolitan France.

But in the last 20 years this notion has had to be revised: as early as 1939, Combe[5] wrote that rheumatic fever and its cardiac complications were far from exceptional in the Mussulman child. Vénezia,[6] in studying the files of the Clinique Medicale d'Alger from 1944 through 1950, showed that the incidence of rheumatic fever (arthritis, chorea, or rheumatic heart disease) was 28 per 1,000 of the Mussulman children of 5 to 15 years of age who were hospitalized during that 7-year period. This figure is comparable to those published by Grenet,[7] in 1949, who reported that in France, of all the children hospitalized in the departments of internal medicine, an average of 20 to 45 per 1,000 had rheumatic fever.

We have resumed this study during the last 8 years, from 1951 to 1958. We have retained only the authentic cases of rheu-

matic fever and purposely omitted the cases of chorea. Our findings show a high percentage of rheumatic fever: about 95 per 1,000.

Although our statistics may be criticized, they undoubtedly reflect an increase in the incidence of rheumatic heart disease. In a hospital ward of 50 patients who ranged in age from 5 to 15 years it is not rare to find that one third of the patients have valvular heart disease.

The second fact to be emphasized is the severity of the disease, as is shown by the frequency of the recurrences and deaths. For a total of 323 patients, we recorded 451 admissions to the hospital; some patients had been admitted several times, some up to seven or eight times during these 8 years. We have recorded 29 deaths, which is a very high figure for a group in which several patients had originally only articular involvements without cardiac manifestations.

Those are the facts. How can they be explained? One might wonder whether the increase in morbidity is not due to the fact that the native more readily seeks medical advice as he becomes adapted to European civilization. But this argument cannot be upheld since the figures reported express the percentage of admissions for rheumatic fever in relation to the total number of admissions in the same hospital. Moreover, the climate, race, and constitutional factors do not seem to have the importance that has been assigned to them by some authors.

Most of our patients are natives of large cities; very few come from the country. The city of Algiers alone provides more than half of the patients. Thus, the most likely cause of the increase in rheumatic morbidity may be found in the economic and social transformation of the Mussulman masses and, consequently, in the demographic evolution of the country. This evolution is characterized by the increase in the native population and the immigration of the rural Mussulman population to the cities.

The native population of Algeria is increasing rapidly: it numbered 3,000,000 individuals in 1830, 7,300,000 in 1948, and 9,250,000 in 1958. The urban population, as represented by the inhabitants of 46 cities, was 226,000 Mussulmans in 1886, 1,398,000 in 1954, and 1,700,000 in 1958. Thus, whereas the total population has increased three times, the urban population was increased eight times. In the city of Algiers the population was estimated to be 13,000 Mussulmans in 1866, 226,000 in 1946, and 420,000 in 1959. The population increases at a rate of 5 per cent annually.

The two consequences of this immigration to the cities are: (1) a dense population often living in conditions of poor hygiene, and (2) a closer relationship of the Mussulman population with the European population which, originally, was more often subject to rheumatic fever.

Actually, since the onset of the disturbances which have troubled Algeria, many "fellahs" (especially peasants) have left the land in order to come and find refuge in the large cities, where they feel more protected from terrorism. And in studying our figures, we see that it is precisely since the year 1954 that the incidence of rheumatic fever has greatly increased.

Can these demographic data explain the severity of the disease in Algeria? Before answering this question, one must wonder whether there is not an "epidemic genius" special to the country. There is no clinical or bacteriologic evidence in favor of this hypothesis. In 1958, Raoux[9] made a complete biologic survey of 51 patients. Each patient was subjected weekly to laboratory studies, including determination of the sedimentation rate, fibrinogen, total polysaccharides, hexosamines, blood and urinary mucoproteins, C-reactive proteins, antistreptolysin titer, proteinogram, lipidogram, and glucidogram. The results were comparable to those published in France and elsewhere in Europe.

Nor can mistakes made in the matter of therapeutics be incriminated, because all of the children received a standard treatment, combining antibiotics and hormones. Treatment of the attack was in each case followed up by maintenance treatment with long-acting penicillin and salicylates. But the prophylactic treatment with penicillin is, in most cases, abandoned as soon as the children leave the hospital. Moreover, these children can-

not find at home the conditions of hygiene and rest required for a complete cure of the disease. Complete bed rest is almost impossible to realize at home.

Thus, the evolution of rheumatic fever in Algeria illustrates strikingly the transformation of the cardiovascular disease in this country. It has given rise to new problems, the importance of which has not escaped the Public Services.

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Clinical communications

Complete left bundle branch block
A physiologic-pathologic correlation
Report of a case

Maurice Lev, M.D.
Chicago, Ill.

We have recently had the opportunity of examining the heart at autopsy of a patient who electrocardiographically showed complete left bundle branch block, and in whom simultaneous catheterization of both ventricles revealed no delay in onset of left ventricular systole. This afforded us the opportunity of studying the conduction system and the entire heart to ascertain the anatomic substrate of this form of complete left bundle branch block.

Case report

Clinical history. This 49-year-old woman was first seen on June 6, 1955, at the clinical center of the National Institutes of Health for evaluation of "rheumatic heart disease." The patient remembered no definite signs or symptoms of rheumatic fever. She did have frequent upper respiratory infections in childhood, which decreased in frequency after tonsillectomy. Six to 8 years before admission she noted insidious onset of shortness of breath. Three years before admission she felt weak, and was treated for "liver trouble and ulcers of the stomach." Her shortness of breath became worse at this time and was accompanied for the first time by ankle edema and ascites. She was placed on digitalis, low-salt diet, and bed rest; and she responded well, until 1 year ago, when she had an episode of pulmonary edema. This responded to treatment and she was well except for shortness of breath on moderately severe exertion.

Physical examination. On this first admission the heart was found to be enlarged to the anterior axillary line. The heart sounds were faint and distinct. The blood pressure was 130/80 mm. Hg. The liver was enlarged. Extensive laboratory examination was essentially negative. The electrocardiogram revealed complete left bundle branch block (Fig. 1). Chest film and cardiac fluoroscopy showed cardiac enlargement lateralward and downward, which was considered to be left ventricular. The aortic arch was smaller than normal. The distal portion of the esophagus was displaced to the right by the ventricular enlargement. An angiocardiogram showed the left ventricle to be grossly enlarged, with no radiographic evidence of a shunt. Left and right heart catheterization showed no evidence of shunt, nor mitral regurgitation or stenosis. Liver biopsy was negative. The patient was discharged on July 20, 1955, being on digitoxin, hexavitamins, phenobarbital, Seconal, and Neohydrin.

She re-entered the hospital on Dec. 19, 1955, because of persistent shortness of breath and fatigue. Physical examination now revealed a blood pressure of 112/62 mm. Hg. A scratchy systolic murmur was heard along the left sternal border, and there was a Grade 2 apical systolic murmur and a questionable diastolic gallop. The liver was again palpable. The ECG again showed complete left bundle branch block.

Simultaneous right and left heart catheterization (Fig. 2) was performed by Dr. Eugene Braunwald, and revealed slight elevation of the right ventricular pressure (32/7 mm. Hg), and marked elevation of the left ventricular end-diastolic pressure to 25 mm. Hg. The time interval between the onset of ventricular depolarization, i.e., the beginning of the QRS complex, and the onset of left ventricular contraction, i.e., the onset of the systolic rise of left ventricular pressure, was 0.075 second. The onset of left ventricular contraction followed the onset of right ventricular contraction by only 0.010 second in some beats, and in other portions

From the Congenital Heart Disease Research and Training Center, Hektoen Institute, Chicago, Ill.
This investigation was supported by Research Grant H3440 from the National Heart Institute of the National Institutes of Health, U.S.P.H.S., Bethesda, Md.
Received for publication June 29, 1960.

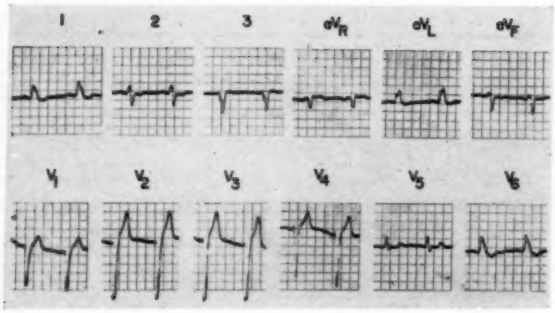


Fig. *1.* Electrocardiogram showing complete LBBB.

of the tracing the onset of contraction in the two ventricles was identical. The duration of left ventricular contraction exceeded that of right ventricular contraction. Normal values for the relationship between electrical and mechanical events were presented by Braunwald, Fishman, and Cournand.[1]

The patient was discharged from the hospital on Jan. 20, 1956, with the diagnosis of idiopathic myocardial hypertrophy. She returned to Miami, Florida, where she was found dead on Feb. 22, 1957. Her history between discharge and death is unknown.

Postmortem examination. Only the heart was available for study (Fig. 3). This weighed 750 grams embalmed. The right atrium was slightly hypertrophied. The tricuspid orifice was markedly dilated. The distance between the orifice of the coronary sinus and the annulus of the tricuspid orifice was enlarged. The edges of the mediəl and anterior tricuspid leaflets showed diffuse thickening which involved the chordae. The right ventricle was slightly hypertrophied, and its chamber was dilated. The pulmonic orifice was slightly dilated and its valve showed increased hemodynamic change. The left atrium was markedly hypertrophied and moderately dilated. The mitral valve showed the usual changes of aging, and the mitral orifice was normal. The left ventricle was tremendously hypertrophied and markedly dilated. The endocardium of the left ventricle was, in general, thicker than normal. In addition, 3 and 5 cm., respectively, from the commissure between the right and posterior aortic cusps, there were two localized thickenings, the proximal one with a diastolic pocket. The aortic orifice was normal in size. As to the aortic valve, the adjacent parts of the right and posterior aortic cusps were thickened, and there was an adhesion between them below where the commissure should have been. There was no exact commissure between the adjoining edges. The remainder of the valve showed the usual changes of aging, with slight widening of the commissure between the left and posterior cusps. The right circumflex and the left anterior descending coronary arteries presented only occasional plaques and no narrowing. The left circumflex could be followed only in its beginning and showed no narrowing.

The internal measurements of the heart were as follows: tricuspid orifice—12.7 cm.; pulmonic orifice—7.5 cm.; mitral orifice—8.0 cm.; aortic orifice—7.0 cm.; right ventricle, inlet length—9.3 cm., outlet length—11.5 cm.; left ventricle, inlet length—9.5 cm., outlet length—10.3 cm.

Microscopic examination. The entire heart, including the conduction system, was studied in a manner previously described.[2] The S-A node and its approaches, the A-V node and its approaches, and the penetrating portion of the A-V bundle were serially sectioned and every twentieth section was retained. The branching portion of the A-V bundle with the origin of both bundle branches were serially sectioned and every tenth section was retained. The remainder of the bundle branches up through the level of the moderator band was serially sectioned and every twentieth section was retained. The bases of the anterior and posterior papillary muscles were serially sectioned and every fortieth section was retained. The region containing the ramus ostii cavae superioris was serially sectioned and every eightieth section was retained. The remainder of the atrial and ventricular septa and the entire parietal walls of the atria and ventricles were cut into blocks, and two sections were taken from each block. These sections were alternately stained with hematoxylin-eosin and Weigert-van Gieson stains. Thus, a total of 1,297 sections were studied.

GENERAL PATHOLOGIC CHANGE. There was an acute vascular degeneration associated with a mild perivascular fibrosis throughout the myocardium of both ventricles, atria, and the atrial and ventricular septa. Occasional macrophages were infiltrated in the perivascular spaces. The fat tissue at the base of the ventricles in the A-V grooves showed a fine infiltration of mononuclear cells, with a growth of young connective tissue. Focal fibroelastic thickening was present in the endocardium of the left ventricle.

Left ventricle, anterior wall: There was subendocardial fibrosis with small scars, more prominent in the apical than in the basal half. This involved the anterior papillary muscle.

Left ventricle, posterior wall: Small zones of subendocardial fibrosis were less numerous here, but the posterior papillary muscle showed considerable fibrosis with small scars.

Right ventricle, anterior wall: There was marked fatty infiltration.

Right ventricle, posterior wall: Aside from the generalized pathology, there was no change.

Ventricular septum: There was an elastosis of the myocardium at the base. The left side of the ven-

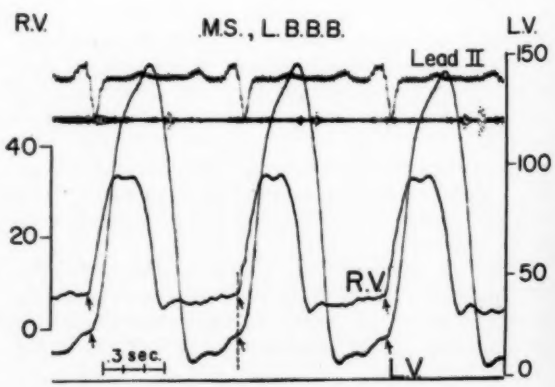


Fig. *2.* Pressure tracing showing no delay in onset of left ventricular systole.

tricular septum showed marked fibroelastic thickening of the endocardium, with scattered accumulations of lymphoid cells beneath the endocardium. Zones of fibrosis and small scars were present beneath the endocardium and were most numerous and large in the mid-anterior and apical portions of the septum. There was an occasional eccentric thickening of an arteriole.

Atria: The left atrium showed foci of lymphoid cells beneath the endocardium. Both atria presented a few such accumulations in the wall. In addition, in the right atrium there was considerable fatty infiltration beneath the endocardium and in the wall, with hemorrhage in the epicardium and myocardium in the appendage. Here, also, there was focal thickening of the epicardium with an infiltration of lymphoid cells.

Aortic valve: There was no evidence of old endocarditis (Fig. 4). Section through the peculiar commissure showed hemodynamic changes[3] with zones of degeneration and small infiltrations of mononuclear cells.

Mitral valve: In addition to the ordinary changes due to aging, the ventricularis at the base of the mitral valve showed proliferation of the endothelial lining and an infiltration of neurtrophils. There was no evidence of old endocarditis.

Tricuspid and pulmonic valves: These showed increased hemodynamic changes, but no evidence of old endocarditis.

Conduction system: S-A node—The node was considerably surrounded by fat, but not isolated. Otherwise no change was noted. Approaches to S-A node—Here there were foci of hemorrhage. Approaches to the A-V node—Here there was a marked infiltration of fat, with a few lymphoid cells and eosinophils. A-V node—Slight fatty infiltration was present. A-V bundle, penetrating and branching—Fatty infiltration was present. An occasional arteriole was narrowed. There was marked fibrosis of the left side of the bifurcation.

Left bundle branch: The changes here were related to the changes in the central fibrous body and the adjacent ventricular septum. The central fibrous body was elongated, and sent large shoots into the base of the ventricular septum in both the left and the right sides. Some calcification was noted on the right side. The pars membranacea likewise showed fibrous thickening, with hyalinization on the left side. On the left side, the endocardial and subendocardial regions of the base of the ventricular septum were thus replaced by thick hyalinized connective tissue (Fig. 5). The beginning of both the anterior and posterior radiations of the left bundle branch was thus interrupted (Fig. 6). Only a few solitary strands of fibers were seen proceeding in this area. Since every tenth section was saved in the serial sectioning of this area, it cannot be stated whether the interruption of the left bundle branch was complete. More distal to this region, fibers of the left bundle branch were seen both in the anterior and the posterior radiations. They appeared to be smaller than normal (Fig. 7), being about the size of myocardial cells. There were zones of fibrosis throughout.

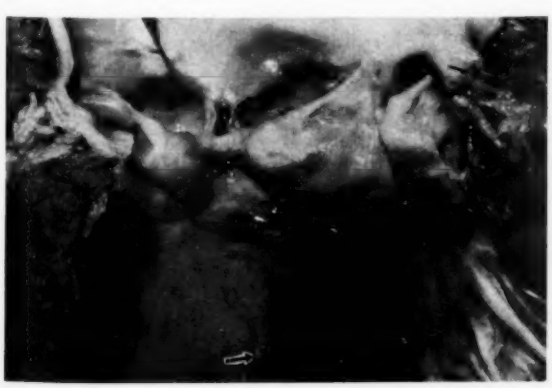


Fig. 3. Aortic valve, showing peculiar cusp formation. Arrow points to jet lesion.

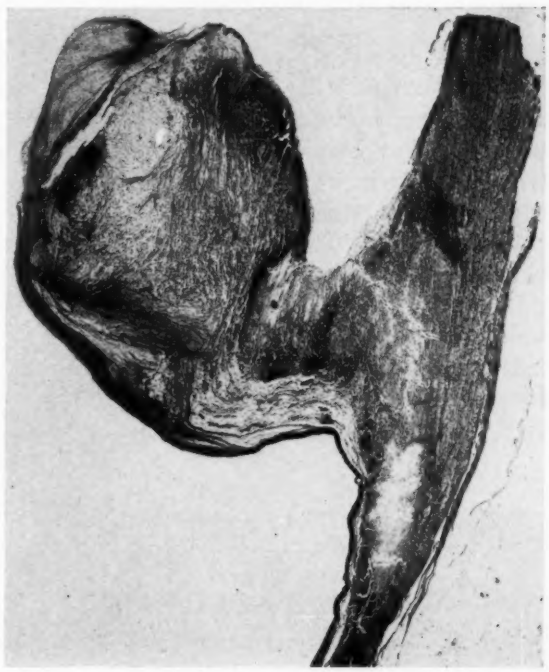


Fig. 4. Photomicrograph of the small cusp-like formation of the aortic valve, showing the coral-reef appearance of the hemodynamic changes. Weigert–van Gieson stain, × 25.

Right bundle branch: The first portion showed occasional small zones of fibrosis which replaced less than one tenth of the muscle in any section. The second and third portions were normal. The right bundle branch was followed into the moderator band.

Pathologic diagnosis of the heart. (1) Congenital malformation of the aortic valve with aortic insufficiency. (2) Focal endocardial fibroelastosis of the left ventricle. (3) Subendocardial fibrosis with small scars of the left ventricle. (4) Hypertrophy and dilatation of the left atrium and ventricle, marked; right ventricle, moderate; and right atrium, slight. (5) Fibrosis of the base of the ventricular septum. (6) Severe fibrosis of the beginning of the left bundle branch. (7) Fatty infiltration of the right ventricle. (8) Subacute inflammation of the fat tissue of the heart. (9) Acute vascular degeneration.

Discussion

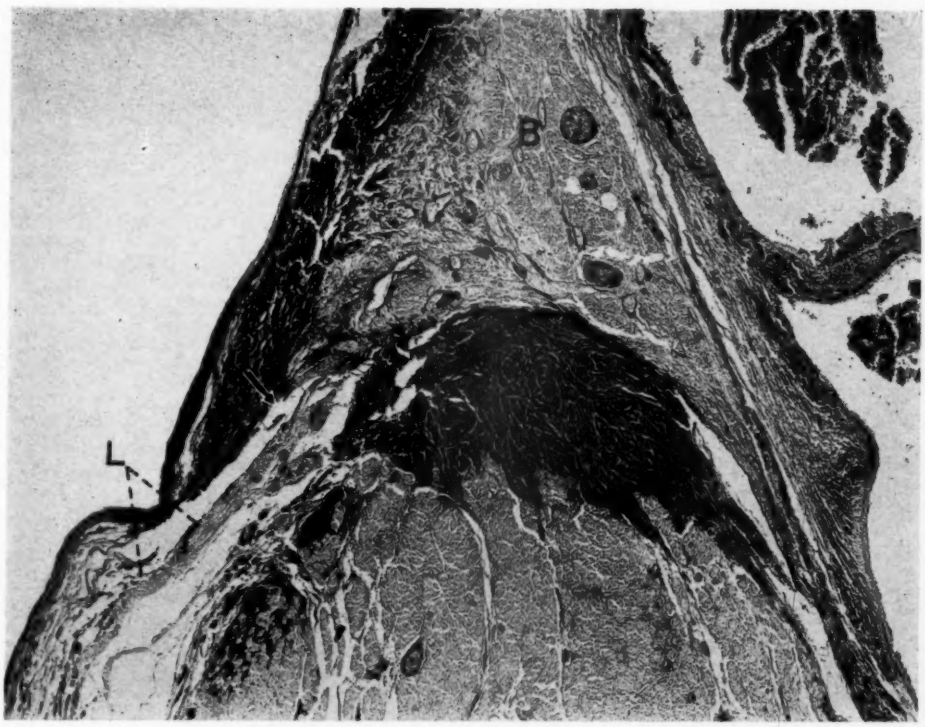
This is apparently a case of an unusual type of congenital malformation of the aortic valve producing unusual effects. The malformation may be considered to be a tricuspid aortic valve with an unusual type of commissure formation or a quadricuspid valve. With advancing years and hemodynamic change, this valve produced mild aortic insufficiency. The abnormal valvular formation, with the insufficiency, had striking hemodynamic effects. It led to focal endocardial hypertrophy (fibroelastosis)[4] and to fibrosis of the central fibrous body and the adjacent base of the ventricular septum. The latter was responsible for the lesion of the left bundle branch.

Fig. 5. Photomicrograph of the base of the ventricular septum. Hematoxylin-eosin stain, ×20. *B:* Bundle of His. S_1: Scar on the left side of the muscular ventricular septum. S_2: Scar on the right side of the muscular ventricular septum. Arrow points to the region of interruption of the posterior radiation of the left bundle branch.

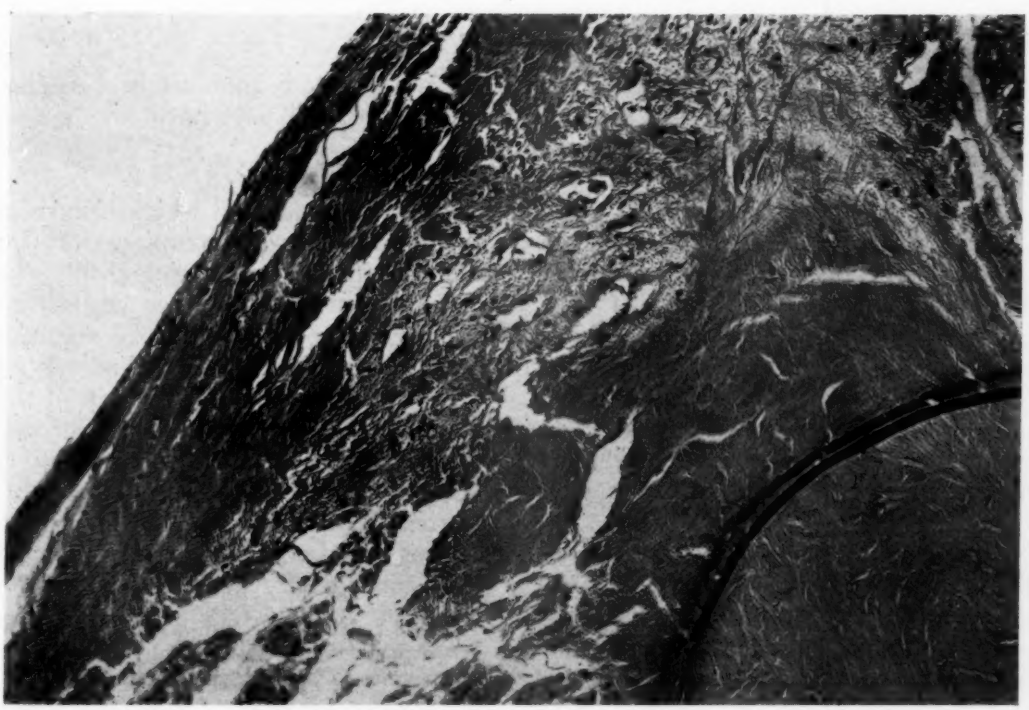
In the absence of coronary disease and healed myocarditis, in our present knowledge a possible cause for the subendocardial fibrosis with scarring of the left ventricle is the fibroelastosis interfering with the arterioluminal and venoluminal circulation of the myocardium. This theory is supported by the much greater presence of both the fibroelastosis and the scarring in the anterior and mid-portion of the septum than in the posterior basal portion of the septum. Thus, an ischemic lesion is postulated to be superimposed on the mild aortic insufficiency, thereby aiding in the production of hypertrophy and failure of the left ventricle. It is possible that another factor in the hypertrophy is the abnormal function of the left ventricle, related to the left bundle branch block.

Concerning the correlation of the left bundle branch lesion with the physiologic findings, it is to be noted that there was no delay in onset of left ventricular contraction. Yet the electrocardiographic findings were those of complete left bundle branch block. However, there was a paradoxical relationship in the closure of the semilunar valves: the pulmonary valve closed before the aortic. Braunwald and Morrow[5] have previously postulated the following hypothesis for the explanation of this: "A conduction block may exist in the branches of the left main bundle or within the left ventricular myocardium. Such a conduction disturbance would account for the prolongation and abnormal configuration of the QRS complex and also for the delay in the onset and termination of ventricular ejection. However, since the onset of left ventricular contraction in these patients is normal, a substantial portion of the left ventricle must begin to contract at a normal time and must therefore be depolarized at a normal time. Thus complete interruption of conduction could not be present."

It is unfortunate that our findings do not represent sufficiently useful data to shed light on this hypothesis. Since every tenth section of the origin of the left bundle branch was studied instead of complete serial sections, we can only state that this was a severe lesion of the left bundle branch



A.



B.

Fig. 6. *A*, Photomicrograph of the base of the ventricular septum at the beginning of the bifurcation. Low-power view. Weigert–van Gieson stain, ×51. *B:* Bundle of His. *L:* Anterior radiation of left bundle branch. Arrow points to the interruption. *B*, High-power view of similar area, showing fibrosis with an infiltration of lymphoid cells. Hematoxylin-eosin stain, ×125.

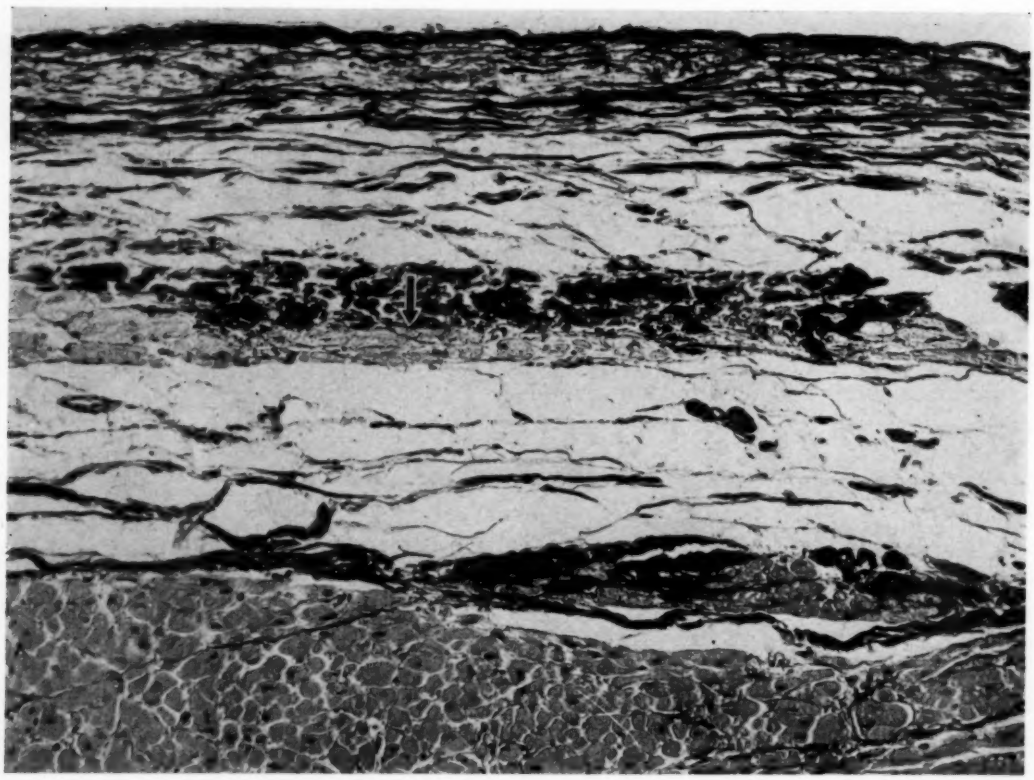


Fig. 7. Photomicrograph of Purkinje fibers of left bundle branch, showing small size. Arrow points to the Purkinje fibers. Weigert–van Gieson stain, ×175.

(90 per cent destruction), but we do not know whether it was a complete lesion. Likewise, possible activation of the septum by Mahaim fibers from the A-V bundle cannot be completely excluded by this study, since every twentieth section was studied in the penetrating portion of the bundle, and every tenth section in the branching portion, instead of complete serial sections. However, no Mahaim fibers were seen in the present method of sampling. Thus, these anatomic studies do not answer the question of complete versus severe interruption of conduction to the left ventricle.

Nevertheless, this case of complete left bundle branch block has a distinct anatomic base. There is severe interruption of the beginning of the left bundle branch, with subendocardial fibrosis and small scars in the hypertrophied and dilated left ventricle involving the papillary muscles. The genesis of this case of interruption of the left bundle branch is in accord with the findings of Lenègre,[6] who suggested that most of these lesions in the beginning of the left bundle branch are of a mechanical rather than ischemic nature.

Conclusion

A case is presented which electrocardiographically showed complete left bundle branch block, and physiologically showed no delay in onset of ventricular systole but delay in onset and termination of ventricular ejection. Pathologically, there was a severe lesion of the origin of the left bundle branch, produced by fibrosis and scarring of the central fibrous body, the pars membranacea, and the base of the ventricular septum. This was apparently related to abnormal hemodynamic effects of a congenitally malformed aortic valve.

I am indebted to Dr. Eugene Braunwald for permitting me to use the catheterization data, the illustrations of the electrocardiogram, and the pressure tracings, and for his interpretation of this data. Also, I wish to thank Mr. Tomas R. Alvarez, B.S., A.S.C.P., for his technical assistance.

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Relationship of elevated blood pressure to ECG amplitudes and spatial vectors in otherwise "healthy" subjects

*Pentti M. Rautaharju, M.D.**
*Henry Blackburn, M.D.***
Minneapolis, Minn.

The electrocardiogram is the most sensitive known indicator of left heart involvement in hypertensive patients, although its specificity leaves something to be desired.[1] Increased QRS amplitude is believed to be the earliest manifestation of left ventricular hypertrophy,[2] followed later by S-T-T changes. We have attempted here to determine whether moderate elevation of arterial blood pressure as often found in apparently healthy men is associated with characteristic differences in conventional electrocardiographic amplitudes and in spatial vectors.

Procedure

The study population consisted of 468 rural Finnish laborers who ranged in age from 20 to 60 years. Preselection involved elimination of respondents in the area who reported any history suggestive of heart disease, murmurs, hypertension, or other major physical impairment. Further selection was made for these items on the basis of findings at the time of medical examination. Indirect blood pressure was recorded at a single sitting, and subjects were included for analysis regardless of an isolated finding of elevated blood pressure if they were asymptomatic.

Blood pressure groups A, B, and C were assigned according to arbitrary cutoff values, following the recommendations of the World Health Organization,[3] and the number of subjects per group, according to age, are presented in Table I, along with relative weight and mean diastolic pressure, which was the value used in correlation analysis. In Group A were all subjects who had both a systolic pressure of less than 140 and a diastolic pressure of less than 90 mm. Hg. In Group B were subjects who had pressures of 140 mm. Hg systolic and/or 90 mm. Hg diastolic, but under 160/95 mm. Hg. In Group C were all subjects who had pressures of 160 mm. Hg systolic and/or 95 mm. Hg diastolic, or over. Eleven men had a systolic blood pressure that exceeded 180, and 12 had a diastolic blood pressure over 100, but no men who had a blood pressure of 200/110 mm. Hg or more were included.

Unipolar chest leads V_{4R} and V_1 through V_6 were recorded at the level of the fifth intercostal space in the mid-clavicular line,

From the Department of Biophysics, and the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

This work was partly done during the tenure of a Research Fellowship from the Minnesota Heart Association, and was supported in part by a research grant from the Finnish Geriatric Association, Helsinki, Finland.

Received for publication June 30, 1960.

*Research Fellow, Department of Biophysics, University of Minnesota; Former Minnesota Heart Association Fellow, Laboratory of Physiological Hygiene, University of Minnesota; and Former Research Fellow, Institute of Occupational Health, Helsinki, Finland.

**Assistant Professor, Laboratory of Physiological Hygiene, University of Minnesota; and Medical Director, Mutual Service Insurance Companies, St. Paul, Minn.

Table I

Age group	*Number of subjects*			*Mean relative body weight (%)*			*Mean diastolic blood pressure (mm. Hg)*		
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
20–29	63	47	22	98.4	103.8	105.0	78	84	96
30–39	64	42	35	99.5	102.8	109.5	79	87	97
40–49	56	34	28	95.8	95.0	107.4	79	85	99
50–59	32	23	22	95.6	96.7	108.1	77	88	100

A: Under 140/90 mm. Hg blood pressure.
B: 140/90–159/94 mm. Hg blood pressure.
C: 160/95–199/109 mm. Hg blood pressure.

and leads to the right of V_{4R} were taken when necessary to secure the T-wave transitional zone. The leads were otherwise conventional, and mean spatial QRS and T vectors were constructed with a mechanical analyzer previously described.[4] Data are given in terms of azimuth, H° (the horizontal plane vector, in which 0 degrees points directly to the left) and elevation, V° (the frontal plane angle representing the vertical elevation in which 0 degrees points straight down and 90° is the horizontal), vector magnitude (with 1.0 mm. = 0.1 mv.), and the spatial angle, dA°, between mean QRS and T vectors.

Results

Table II presents amplitudes of the R and T waves in Lead V_5, and the magnitude of mean QRS and T vectors in the blood pressure groups. There is a slight trend toward higher QRS amplitude and lower T amplitude of conventional measurements in Lead V_5 according to higher blood pressure categories. The vector magnitudes also show differences between lowest and highest blood pressure groups, but without a consistent trend. In no case is the mean difference statistically significant except for the T wave in Lead V_5, which is significantly lower in the high-pressure Group C than in Group A.

Correlation between the amplitudes of the T and R waves in Lead V_5 is expressed by regression equations as follows:

Group A: $T_{V5} = 2.4 + 0.130 \times R_{V5}$
Group B: $T_{V5} = 2.5 + 0.106 \times R_{V5}$
Group C: $T_{V5} = 1.8 + 0.099 \times R_{V5}$

There is no significant difference in the slopes, but the difference in intercept between lower and higher blood pressure groups (A and C) is statistically significant ($p < 0.01$).

Table III presents the data for azimuth (H°) and elevation (V°) of mean QRS and T vectors and the spatial angle between these vectors (dA°), according to blood pressure grouping, and the statistical significance of mean differences between the lower and higher blood pressure categories (C-A).

There is no significant difference between groups in spatial orientation of QRS and T in the horizontal plane. The angle of elevation of both QRS and T vectors is greater in the higher blood pressure group, corresponding to a more "horizontal electrical position." The spatial angle of separation of mean QRS and T vectors is significantly greater in the higher pressure category (C).

The relationship of QRS elevation angle (V°) and age is given in Fig. 1 for Groups A and C. There is a significant though small positive correlation in elevated pressure in Groups B ($r = 0.287$) and C ($r = 0.236$) but none in Group A ($r = 0.122$).

Analysis of the relationship of QRS elevation angle (V°) and relative body weight reveals a significant positive correlation within blood pressure Group C ($r = 0.372$), but none in the "normotensive" Group A ($r = 0.129$) or in blood pressure Group B ($r = 0.133$).

Analysis of the QRS elevation angle (V°) in regard to age, when relative body weight is kept constant, reveals the persistence of a significant positive correlation in subjects with elevated blood pressure: Group B ($r = 0.265$), Group C ($r = 0.252$), but none in Group A ($r = 0.093$).

Correlations between the elevation of the

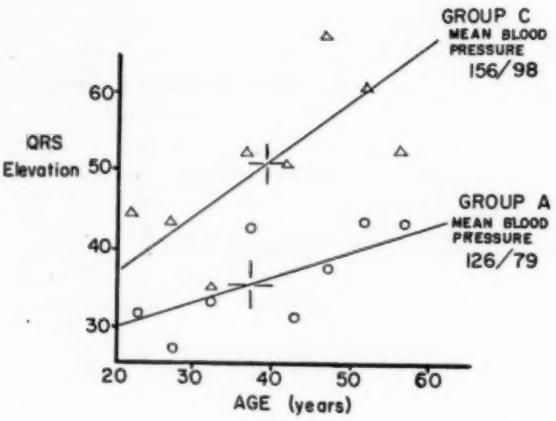

Fig. *1*.

QRS vector (V°), age, and relative body weight are expressed by regression equations as follows:

Group A: $V° = -23.3 + 0.46 \times \text{Age} + 0.42 \times \text{Relative Weight}$

Group B: $V° = -41.7 + 0.81 \times \text{Age} + 0.49 \times \text{Relative Weight}$

Group C: $V° = -52.0 + 0.64 \times \text{Age} + 0.77 \times \text{Relative Weight}$

Fig. 2 shows the relationship of diastolic blood pressure and the angle between QRS and T vectors (dA°) for the entire sample of 468 "healthy" men. The correlation coefficient of this regression is 0.389. A significant positive correlation between this spatial angle (dA°) and relative body weight ($r = 0.244$) is found and, as well, between relative weight and diastolic blood pressure ($r = 0.369$). However, when diastolic pressure is kept constant there is no longer a significant correlation between the spatial angle (dA°) and relative weight. And when the body weight is kept constant, the significant positive correlation between diastolic blood pressure and the spatial angle dA° persists ($r = 0.332$).

Discussion

Attempts to apply criteria of ECG amplitudes in the individual diagnosis of left ventricular hypertrophy may result in considerable error, in both missed and false-positive diagnoses.[1] In general, however, among adult men, a clinical relationship exists between large QRS waves, low T waves, and advanced hypertension. Recently, Libretti and Zanchetti[5] studied a group of hypertensive patients with blood pressure over 200/110 mm. Hg, and found that correlations which normally exist between QRS and T vectors decrease more or less in parallel with the severity of heart involvement. The data presented here suggest that a lower order of blood pressure elevation, in putatively healthy working men, results in myocardial changes of the same type but of lesser magnitude. The ECG findings in the higher pressure groups include significantly lower T-wave amplitude, a significant difference in the intercept of the correlation between amplitudes of the R and T waves in Lead V_5, increased elevation of QRS and T vectors, and increased spatial angle between QRS and T vectors (dA°). The spatial angle between QRS and T vectors (dA°) is larger in subjects with elevated blood pressure in all age groups, and there is also a definite regression toward a larger angle with progressive increase in diastolic blood pressure ($dA° = 30.8 + 0.32 \times$ diastolic blood pressure; Fig. 2). These findings may be the first sign of myocardial involvement in hypertension, and appear prior to any significant increase in the magnitude of R waves or of the QRS vector.

Some of the ECG differences in higher blood pressure groups might be considered to be due to the influence of relative body weight, but statistical exclusion of the effects of relative body weight does not significantly alter the influence of blood pressure. However, the fact that there is a significant correlation between relative body weight and the QRS elevation angle only in the group with blood pressure over

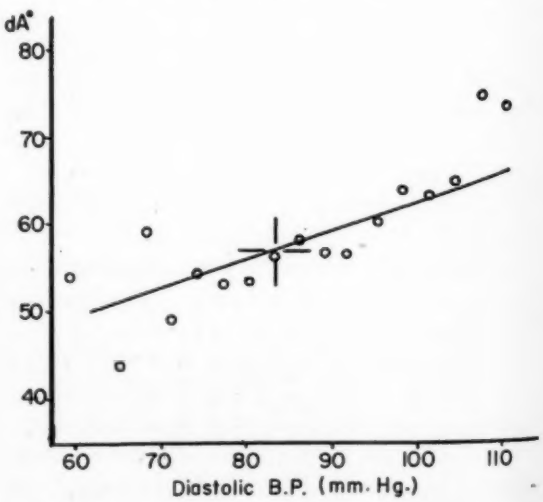

Fig. *2*.

Table II. *R and T wave amplitudes in chest lead V_5 (in mm.), and magnitudes of the mean QRS and T vectors as related to the level of blood pressure*

	Number of subjects	R_{V5} *(mm.)*		T_{V5} *(mm.)*		*Magnitude of QRS*		*Magnitude of T*	
		Mean	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*
Group A	215	18.3	6.16	4.8	2.05	10.4	4.49	3.6	1.36
Group B	146	19.5	6.69	4.6	2.16	10.2	3.91	3.6	1.32
Group C	107	20.4	6.23	3.8	2.00	10.7	3.54	3.3	1.37
Total	468	19.1	6.39	4.5	2.11	10.4	4.07	3.5	1.35

A: Under 140/90 mm. Hg blood pressure.
B: 140/90–159/94 mm. Hg blood pressure.
C: 160/95–199/109 mm. Hg blood pressure.

Table III. *Mean QRS and T vectors, azimuth (H°) and elevation (V°), and the spatial angle between them (dA°) in 468 healthy men, aged 20 to 60 years, subdivided into three groups according to the blood pressure*

	QRS-H°		*QRS-V°*		*T-H°*		*T-V°*		*dA°*	
	Mean	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*	*Mean*	*S.D.*
Group A	−28.4	15.4	33.9	17.5	+49.7	7.0	53.1	17.3	53.8	27.8
Group B	−27.1	18.7	37.3	25.5	+49.2	8.8	59.3	19.2	57.0	18.7
Group C	−26.4	15.4	51.0	28.9	+48.9	8.3	58.7	22.1	63.9	18.4
Total	−27.6	16.4	39.3	28.1	+49.3	8.5	56.6	18.6	57.7	18.5
ΔC-A*	+2.0		+17.1		−0.8		+5.6		+10.1	
t*	1.10		5.06		0.78		2.30		5.36	
p	0.05		0.001		0.05		0.05		0.001	

*Differences of the means between Groups A and C (ΔC-A) and their significances as evaluated by the t-test.
A: Under 140/90 mm. Hg blood pressure.
B: 140/90–159/94 mm. Hg blood pressure.
C: 160/95–199/109 mm. Hg blood pressure.

160/95 mm. Hg speaks in favor of a summation effect of elevated blood pressure and obesity. But it must be noted that relative body weight is a rather poor index for obesity. In general, our results of the effects of relative body weight are in agreement with those of Simonson and Keys.[8]

It may be of particular interest that the "normal age trend"[7,8] toward a more horizontal heart position is found only in groups with "elevated" blood pressure (over 140/90 mm. Hg). Furthermore, differences according to blood pressure in the angle between QRS and T vectors (dA°) and in the ratio of R and T amplitude are in a direction opposite to those found in subjects with sustained high levels of physical activity.[9,10]

Whatever the mechanism, asymptomatic elevation of blood pressure is related to manifest ECG and vectorcardiographic differences of statistical and, very likely, of biological significance. The differences are in the direction of those electrical features associated with myocardial hypertrophy and ischemia, and are probably the first manifestation of the effect of ventricular myocardial work against an increased head of arterial pressure.

Summary

ECG amplitudes and mean spatial vectors are analyzed according to levels of blood pressure in three blood pressure groupings among a sample of putatively healthy laborers who ranged in age from 20 to 60 years (Group A—under 140/90 mm. Hg blood pressure; Group B—140/90 to 159/94 mm. Hg blood pressure; and Group C—160/95 to 199/109 mm. Hg blood pressure).

In the groups with asymptomatic moder-

ate elevation of blood pressure, significant differences from the "normotensives" are found, with lower T-wave amplitude, greater elevation of QRS and T vectors, and a widened spatial angle between QRS and T vectors. The differences are not due principally to the effect of overweight. The "normal age trend" toward a horizontal electrical heart position is *not* apparent in the "normotensive" group. The ECG and vectorial differences found are in the direction of those electrical features which characterize myocardial hypertrophy and ischemia, and they probably represent the earliest ECG signs of the myocardial effect of an increased cardiac work load.

The suggestions and criticism of Professor Ernst Simonson of the Laboratory of Physiological Hygiene are appreciated.

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An experience with transseptal left heart catheterization

*Charles J. McGaff, M.D.**
*George C. Roveti, M.D.***
*Ephraim Glassman, M.D.****
Richard S. Ross, M.D.
Baltimore, Md.

The value of a new method of cardiovascular diagnosis is enhanced by evidence that it can be employed successfully by individuals other than those responsible for its development. Ross[1,2] and his co-workers[3-5] have developed an approach to the left atrium by puncturing the interatrial septum from the right atrium. This method has been successfully employed by them in 130 patients.[6] Dr. Eugene Braunwald kindly instructed us in this technique, and our experience in 55 patients is reported here.

Method

The 55 patients were between the ages of 9 and 59 years and had a variety of cardiovascular diseases, as listed in Table I. All patients were fasting and received intramuscular morphine, 10 to 15 mg., and pentobarbital, 100 mg., as premedication. The procedure was performed as described by Ross and associates, with only minor modifications. Whenever possible, a large tributary of the right saphenous vein was used in order to save the saphenous vein and thus preserve it for a subsequent transseptal procedure. Occasionally, the catheter would not pass the junction of the right common iliac vein with the inferior vena cava. This difficulty could usually be overcome by bending the patient's trunk to the left, thus making the angle of venous junction less acute, or by placing the transseptal needle in the catheter to give a curve to the catheter tip which would facilitate manipulation.

Simultaneous catheterization of the pulmonary artery was accomplished through the right arm in 26 cases for diagnostic or investigative procedures.[7,8] For these studies, the exploring polyethylene catheter was placed in the left atrium, and the transseptal needle was completely withdrawn into the large catheter in the right atrium. In several cases the large catheter and the puncturing needle were completely removed from the body, and the small polyethylene catheter was allowed to remain in the left atrium, in order to permit simultaneous catheterization of the pulmonary artery through the saphenous vein. In 9 cases the right heart was catheterized from the saphenous vein after completion of the left heart study.

In 5 instances in which the left ventricle

From the Departments of Medicine and Surgery, The Johns Hopkins University and Hospital, Baltimore, Md.
Supported in part by Life Insurance Medical Research Fund Grant G-58-13, and by United States Public Health Service Grant H-226.
Received for publication July 5, 1960.
*Fellow of the National Foundation; presently at University of Louisville School of Medicine, Louisville, Ky.
**Fellow of the Heart Association of Maryland.
***Fellow of the National Heart Institute.

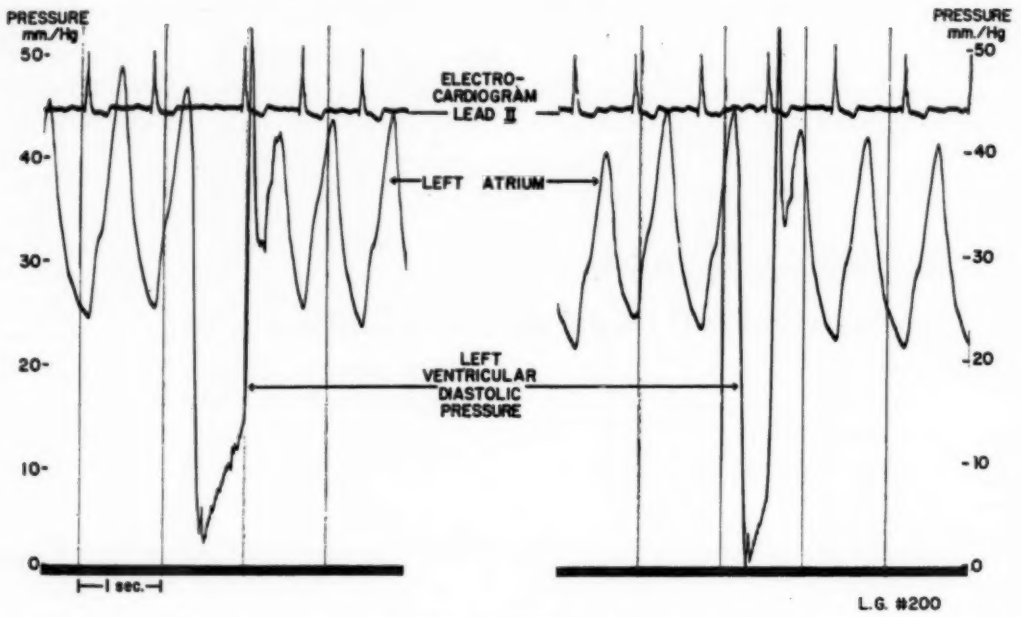

Fig. *1.* Two strips of pressure tracing from a patient with mitral stenosis and regurgitation. In both, the catheter transiently entered the left ventricle, and ventricular diastolic pressure was recorded. The catheter was then washed back into the left atrium at the onset of ventricular systole, and ventricular systolic pressure was not recorded. Left atrial pressure precedes and follows the left ventricular diastolic pressure, allowing measurement of the mitral valvular diastolic pressure gradient.

could not be entered with the polyethylene catheter, left ventricular puncture was performed as described by Brock,[9] and simultaneous left ventricular and left atrial pressures were recorded. In patients with aortic stenosis in whom high-fidelity recording of the left ventricular pressure was essential, a sterile strain gauge was connected directly to the catheter in the left ventricle in order to avoid the damping effect of long segments of polyethylene tubing. Cardiac output was determined by the indicator dilution technique in 49 cases by injection of indocyanine green into the left atrium or into the pulmonary artery.

Results

The diagnoses, number of attempts, and number and percentage of successful catheterizations are shown in Table I. In 2 patients the inferior vena cava, and therefore the heart, was not entered, and thus these attempts were not included in the calculation of the percentage of successful entries into the left atrium. One of these patients had anomalous veins in both groins and had had prior ligation of the right saphenous vein for varicosities. The catheter was passed several centimeters up the left femoral vein but could not be advanced any farther. In the other patient the catheter could not be manipulated past the junction of the right common iliac vein with the inferior vena cava.

In 2 subjects the interatrial septum could not be punctured. One of these patients with mitral stenosis had a very large right atrium, and the puncturing needle did not touch the septum. There is no explanation for the failure in the other patient, who had aortic stenosis, except that the procedure was done early in this series. The left atrium was punctured in 51 of the 53 cases in which the right atrium was entered (96 per cent). On several occasions after septal puncture, pressures were recorded which were presumably from the left atrium. The needle could easily be flushed, but a sample of blood could not be aspirated, and the polyethylene catheter could not be advanced past the needle tip. It is postulated that in these cases the needle may have been partially occluded by left atrial thrombi. One of these patients was operated upon, and a thrombus was present in the left atrium in the region of the interatrial septum.

The left ventricle was entered in 73 per

cent of all the cases in which the left atrium was entered. When moderate or severe mitral regurgitation was present, the flimsy polyethylene catheter usually washed back into the atrium with each ventricular systole, and the lowest percentage of successful left ventricular catheterizations was carried out in the subjects with mitral regurgitation. In spite of this "wash-out phenomenon" an occasional good ventricular diastolic pressure recording could be obtained before the catheter was washed back into the atrium during ventricular systole. This was interpreted as successful left ventricular catheterization, since the diastolic pressure gradient across the mitral valve could be determined. An example of this is shown in Fig. 1. In 5 cases in which the left ventricle was not entered by the exploring catheter, apical puncture was performed.

The cardiac index varied from 1.03 to 5.23 L./min./M.^{2}, mean 2.7 L./min./M.^{2}. There were 14 patients with an elevated pulmonary vascular resistance. Neither of these parameters influenced the success or failure of the procedure.

Discussion

Ross and his co-workers[1-5] have shown that the transseptal method of left atrial puncture is a safe, useful, and readily applied technique. The experience reported here confirms their observations, and the results are similar.

The procedure is simple and easy to perform. The majority of these catheterizations have been performed by six physicians who are research fellows. The technique does not require the attendance of a trained endoscopist or a thoracic surgeon. The hemodynamic information obtained has been useful in physiologic investigations and in preoperative and postoperative assessment of valvular lesions. The subject is comfortable, quiet, and without pain. To our knowledge, neither the aorta, the pleura, the mediastinum, the right ventricle, nor the coronary sinus has been entered. There has been no evidence of hemothorax, pneumothorax, or hemopericardium. There have been short runs of ventricular premature contractions when the polyethylene catheter was in the left ventricle, and these have been promptly terminated by withdrawal of the catheter. There have been no serious complications after the procedures.

Table I. *Results of transseptal catheterization*

*Diagnosis**	*Number of patients*	*Left atrium entered*	*Left ventricle entered*
MS	18	17 (93%)	11 (65%)
MR	12	12 (100%)	7 (58%)
MR with MS or with AS or AR	11	11 (100%)	9 (82%)
AS with or without AR	6	5 (83%)	5 (100%)
NR	4	4 (100%)	4 (100%)
LVF	2	2 (100%)	1 (50%)
Total	53	51 (96%)	37 (73%)

*MS: Mitral stenosis. MR: Mitral regurgitation. AS: Aortic stenosis. AR: Aortic regurgitation. NR: Normal. LVF: Left ventricular failure.

Summary

The safety and value of the transseptal technique of left heart catheterization previously reported from the National Heart Institute has been confirmed in 55 patients studied at the Johns Hopkins Hospital.

The authors gratefully acknowledge the collaboration of E. Battersby, M.D., D. Azevedo, M.D., and C. R. Cooke, M.D., and the technical assistance of Misses Gretchen Sause, Anna May Yung, and Rosemary Gross.

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Left-heart volumes in coarctation of the aorta

*Ivan L. Bunnell, M.S., M.D.**
*Danae Ikkos, M.D.***
*Ulf G. Rudhe, M.D.****
*H. J. C. Swan, M.B., M.R.C.P., Ph.D.*****
Stockholm, Sweden

Angiocardiography has been used in estimating chamber volumes of the left atrium and ventricle in experimental animals[1-5] and in patients.[2,6] This report presents some estimates of left atrial and left ventricular volumes in coarctation of the aorta which were made with the use of the technique of Arvidsson.[6] These observations suggest that in cases of coarctation of the aorta without evidence of cardiac failure (1) ventricular ejection is efficient, leaving a small residual volume (30 per cent of end-diastolic volume), (2) changes of left atrial volume during a cardiac cycle are small in comparison with those of the ventricle, and (3) findings in repeat studies made after surgical repair of the coarctation do not differ significantly from preoperative values.

Material and methods

Seven patients with coarctation of the aorta were studied at the Children's Clinic of the Karolinska Sjukhuset. In three cases both preoperative and postoperative angiocardiograms were available for study, making 10 studies in all. The vital statistics for each patient are given in Table I.

Children who were less than 7 years of age were given basal anesthesia with tribromoethanol (Avertin), and older children received morphine and scopolamine as premedication. During angiocardiography, light intravenous barbiturate anesthesia was administered. Succinylcholine (1 mg. per kilogram of body weight) was given intravenously to inhibit respiration; the anesthetist maintained pulmonary ventilation, using oxygen. Just before injection of contrast the lungs were inflated gently, with pressure of no more than 10 cm. of water in the face mask. Acetrizoate (Urokon), 70 per cent in a dose of 1.2 ml. per kilogram of body weight, was the contrast material used in seven investigations, and diatrizoate methylglucamine (Urografin), 76 per cent in a dose of 2 ml. per kilogram of body weight, was utilized in the other three. The medium was injected into the main pulmonary artery in 1.5 to 2 seconds.

From the Children's Clinic, Karolinska Sjukhuset, Stockholm, Sweden.
Received for publication July 5, 1960.

*Principal Clinical Physiologist, Cardiac Investigation Laboratory, Buffalo General Hospital. Assistant Professor of Medicine, University of Buffalo School of Medicine, Buffalo, N. Y.; Commonwealth Fund Fellow; Visiting Research Associate, Children's Clinic, Karolinska Sjukhuset.
**In charge of Cardiology Department, Children's Clinic, Karolinska Sjukhuset.
***Associate Professor of Radiology, and Chief, Roentgen Diagnostic Department, Children's Clinic, Karolinska Sjukhuset.
****Consultant, Section of Physiology, Mayo Clinic; Assistant Professor of Physiology, Mayo Foundation; Graduate School, University of Minnesota, Rochester, Minn.; Visiting Research Associate, Children's Clinic, Karolinska Sjukhuset.

Table I. *Estimates of left-heart volumes, with other physiologic data in 10 studies of seven patients with coarctation of aorta*

Case	Status	Age, Sex	Height (cm).	Weight (Kg.)	Body surface (sq.M.)	Blood pressure* (mm. Hg)		Pulmonary artery		Heart rate (beats/min.)	Estimated heart volumes (ml./sq.M. body surface)							Cardiac index§ (L./min./M.²)
											Left atrium†‡			Left ventricle†				
						Arm	Leg	Pressure (mm. Hg)	O_2 saturation (per cent)		ESV	EDV	SV	ESV	EDV	SV	ESV / EDV	
1.	Preop.	7, M	116	19.4	0.79	170/114	0	34/10	67	151	28	14	14	30	75	45	.40	6.8
	Postop.	13, M	146	29.2	1.11	155/90	135/83	—	—	146	21	9	12	24	73	49	.33	7.1
2.	Preop.	7, M	121	25.0	0.92	120/80	0	26/10	67	108	25	15	10	17	72	55	.24	5.9
	Postop.	11, M	141	37.7	1.23	135/64	92/73	—	—	116	30	10	20	27	69	42	.39	4.9
3.	Preop.	7, F	116	20.2	0.82	125/75	0	22/9	72	140	30	16	14	17	55	38	.31	5.3
	Postop.	12, F	142	32.7	1.13	125/93	125/88	—	—	165	32	11	21	21	65	44	.32	7.2
4.	Preop.	5, F	101	13.8	0.62	150/100	110/90	18/7	69	115	25	7	18	15	62	47	.24	5.4
5.	Preop.	6, F	117	21.5	0.83	130/80	75/0	16/5	83	78	33	17	16	16	75	59	.21	4.6
6.	Preop.	9, M	135	31.5	1.07	150/110	0	26/4	71	145	35	20	15	10	56	46	.18	6.6
7.	Preop.	7, F	120	22.2	0.84	145/60	0	20/8	64	186	24	14	10	13	47	34	.28	6.3
Averages											28	13	15	19	65	46	.29	

*Preoperative blood pressures were measured by the cuff method; postoperative, by intra-arterial needle.
†ESV: End-systolic volume. EDV: End-diastolic volume. SV: Stroke volume.
‡For the left atrium the values refer to the volumes at the end of ventricular systole and of ventricular diastole. The "stroke volume" of the left atrium is the difference between these values and is a reasonable estimate of the maximal change in left atrial volume.
§Product of heart rate and left ventricular stroke volume.

A program was selected to provide six pictures per second during left-heart opacification, using a roll film changer of the Gidlund type, with simultaneous exposures in the anteroposterior and lateral planes.

Requirements for inclusion of patients in this analysis were absence of cardiac irregularities during the angiocardiographic examination, and a total of at least 14 pairs of frames in which the left atrium and left ventricle presented clear outlines. The sequence under examination therefore included four to eight separate cardiac cycles extending over a period of 2.5 to 4.0 seconds. Simultaneous recording of an electrocardiogram with the exposures provided the means whereby each frame could be related to the events of the cardiac cycle. The exposure times in this series never exceeded 0.023 second (1/45 second). Outlines of the chambers of the left heart were drawn with an accuracy of ± 1 mm. (Figs. 1 and 2).

Analysis for estimation of the volumes of the left atrium and the left ventricle was carried out by the method of Arvidsson[6] in which it is assumed that the shapes of the chambers do not differ appreciably from an ellipsoid.

The measurements used are readily evident from Fig. 1. The volume of the left atrium, V_{LA}, was calculated from the relation

$$V_{LA} = \frac{a}{f_1} \cdot \frac{b}{f_1} \cdot \frac{c}{f_2} \cdot \frac{4}{3^{\pi}}$$

where a, b, and c are atrial semiaxes, in centimeters, and f_1 and f_2 are magnification factors of 1.2 and 1.3, respectively; and hence

$$V_{LA} = (a\ b\ c)\ (2.24) \qquad \text{(Equation 1)}$$

The volume of the left ventricle, V_{LV}, was calculated from the equation:

$$V_{LV} = \frac{L}{2} \cdot \frac{B}{2f_1} \cdot \frac{C}{2f_2} \cdot \frac{4}{3^{\pi}}$$

where B and C are axes of the ventricle, and L, the true long axis of the ventricular ellipsoid,[6] is equal to

$$L = \sqrt{\left(\frac{D \cdot \cos\beta}{f_1}\right)^2 + \left(\frac{A}{f_2}\right)^2}$$

The magnification factors f_1 and f_2 are the same as for the atrial estimation, and β is the angle formed by the ventricular axis projection in the lateral view with the horizontal plane; hence

$$V_{LV} = (L\ B\ C)\ (0.336) \qquad \text{(Equation 2)}$$

Individual estimates of left atrial and left ventricular volumes were plotted against time expressed in fractions of seconds after the R wave of the ECG. From these values, end-diastolic, end-systolic, and stroke volumes were obtained. Since direct measurements of cardiac output were not available, it was calculated as stroke volume times heart rate.

Findings

Mean values for the series are given in Table I. The volumes obtained in each case are plotted in the composite Figs. 3 and 4, each point representing one frame. Of necessity, the individual points plotted at nearly the same times were obtained from different cardiac cycles.

Although data from several cardiac cycles are condensed into one representative cycle, there is relatively little scatter of individual left ventricular volumes. During late systole and late diastole the scatter is minimal. The averages for end-diastolic, end-systolic, and stroke volumes of the left ventricle were, respectively, 65, 19, and 46 ml. per square meter of body surface. From the product of left ventricular stroke volumes and heart rates, cardiac outputs were calculated. Expressed as cardiac indices, these values range from 4.6 to 7.2 L./min./M.^{2}. In general, the subjects with the highest calculated flow rates had the most rapid heart rates.

The changes of volume for the left atrium were much less marked. No variation of a magnitude comparable to that of the stroke volume of the ventricle could be detected. The atrial volume averaged 28 ml./M.^{2} at the end of ventricular systole, and 13 ml./M.^{2} during diastole and early systole. No consistent presystolic decrease in left atrial volume could be identified.

Comment

Accuracy of estimation of volumes. In his study of adult patients with mitral disease, Arvidsson[6] considered on the basis of mathematical analysis that the maximal error inherent in the application of his method to the determination of left atrial volume was

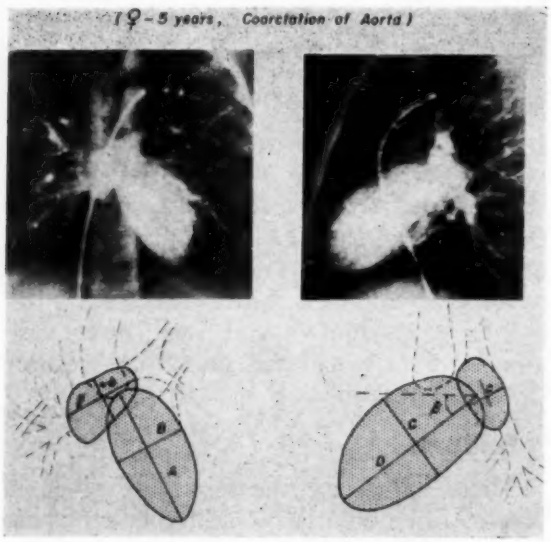

Fig. *1.* Paired angiocardiograms (posteroanterior and lateral projections) obtained during ventricular diastole. Calculations of heart volumes are made as described in the text from the dimensions marked on the line drawings below. In these the lower case symbols refer to semiaxes and the capitals to axes.

approximately ±8 per cent. No experimental comparisons were available for testing such errors. Possible errors due to oblique orientation of the atrium are of an order of magnitude which, according to Arvidsson's analysis, is to be considered small. The shape of the atrium, however, needs special attention. Whereas Arvidsson's investigation was concerned with dilated atria, ours was concerned with atria that were probably undistended or only slightly distended (Fig. 1), and thus were less regular ellipsoids. Consequently, the percentage errors in our estimates of volume may have been greater than in his.

Our errors of measurement were tested by animal experiments in collaboration with Nordenström.* Three dogs which weighed from 8 to 30 kilograms were taken after other experiments, killed, and subjected to thoracotomy. A glass funnel was tied into the left atrial appendage, and through it Wood's metal (melting point, 64°C.) was poured to fill the left atrium, left ventricle, and pulmonary veins. The thorax then was closed, the animal was suspended in a sling, and posteroanterior and lateral roentgenograms of the solid radiopaque cast were obtained. The cast was removed from the animal, the myocardium was dissected free, and the portions which filled the pulmonary veins were cut off at their junction with the atrium. The volumes of these casts were measured by water displacement and compared with three or four paired roentgenograms on which the outline of the casts were measured by different observers. The volumes of the casts measured 21, 44, and 82 ml.; and in all but two instances the estimate based on each film pair agreed within 3 per cent, the exceptions being −9 per cent and −6 per cent for the largest heart specimen. Separate estimates of atrial and ventricular volumes could not be made.

These observations, made in dogs and with the use of a high-contrast object, support the thesis of Arvidsson[6] and of Gribbe and associates[3] that the geometry of a simple ellipse provides a basis for accurate and practical estimation of the volume of cardiac chambers. Theoretical considerations suggest that, if errors are present, the computed values exceed the actual. It should be mentioned that Gribbe[4] has found good agreement in stroke volume as determined by both the direct Fick method and angiocardiography in dogs.

During diastole, overlap between the

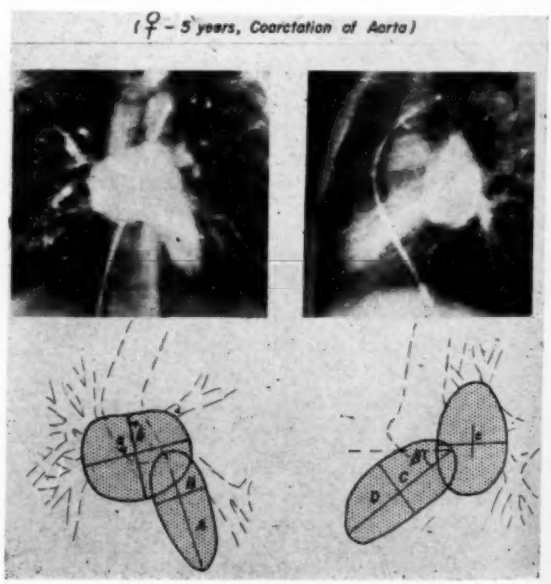

Fig. *2.* Paired angiocardiograms (posteroanterior and lateral projections) obtained during ventricular systole. Note the large dimensions of the left atrium in the posteroanterior as compared to the lateral projection in relation to the change from Fig. 1.

*Dr. Bjorn Nordenström, Chief of the Roentgen Diagnostic Department, Thoraxklinik, Karolinska Sjukhuset.

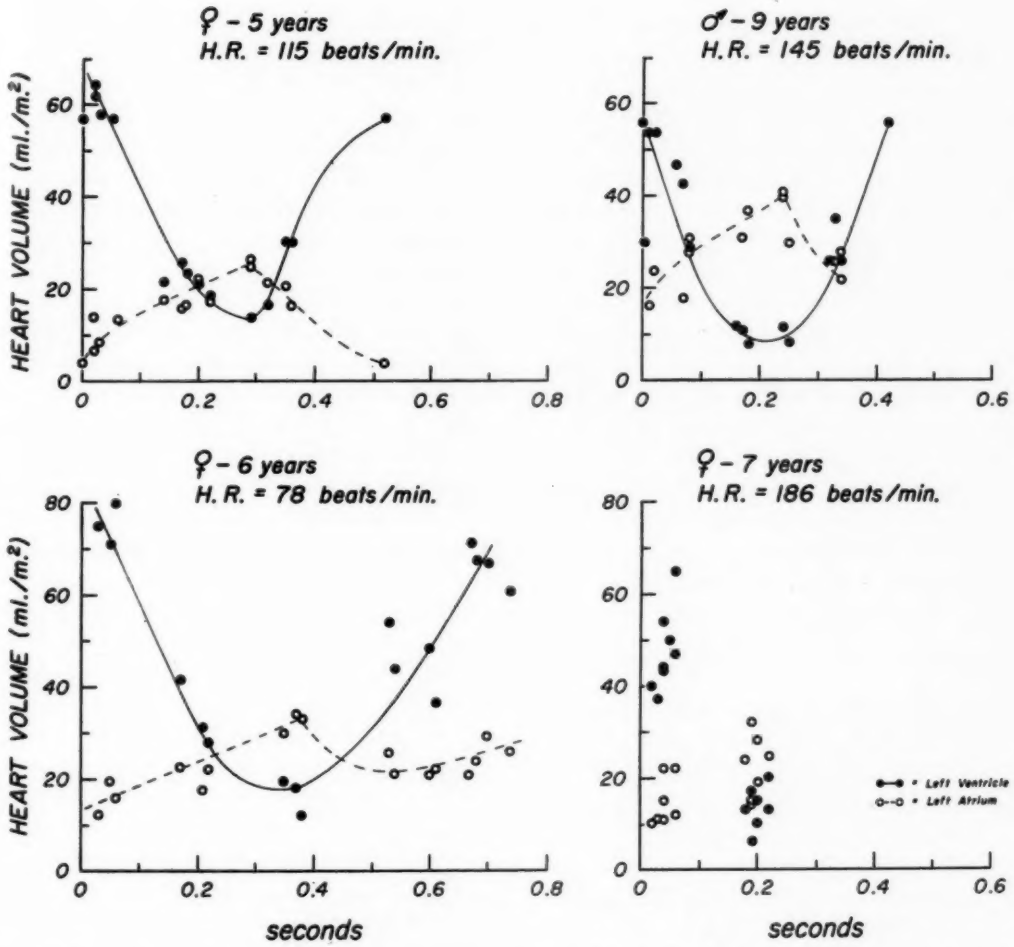

Fig. 3. Changing volumes (milliliters per square meter of body surface) of the left ventricle and left atrium in Cases 4, 5, 6, and 7. The solid lines indicate approximately the continuous volume curves. No line has been inscribed in the panel for Case 7, because a chance synchronization between the filming rate and heart rate prevented a suitable dispersion of the volume estimates.

outlines of the left atrium and the left ventricle is obvious. In children with coarctation of the aorta, however, the volume of overlap can be shown by measurement to be of the order of 1 or 2 ml. Since this is so small, the correction has been neglected in the present study. Since the volume of the papillary muscles was thought not to affect the stroke volumes, this factor was also neglected. In the experiments of Gribbe and associates[3] on dogs the volume of the papillary muscles and the trabeculae carneae was estimated in cast studies. No such information was available in the present study.

Frames exposed at closely comparable times in different cardiac cycles allowed, in our investigation, comparison of estimates of volumes based on chamber outlines of widely different contrast. Although the frames obtained early in the sequence were of much higher contrast than those obtained later, there was no systematic difference between the volumes calculated from early and late exposures.

Opacification of the left heart was discernible in an average of seven cardiac cycles (range, 6 to 14). This would tend to minimize the potential effect of the addition of the injected volume of contrast on the size of the left heart. The addition of such a substantial volume, however, would be to increase the apparent volume of fluid passing through the chambers of the left heart by approximately 10 per cent.

Physiologic considerations. An approach to the determination of the efficiency of left ventricular ejection can be made by considering the volume of blood left at the end of systole (Table I). If preoperative and

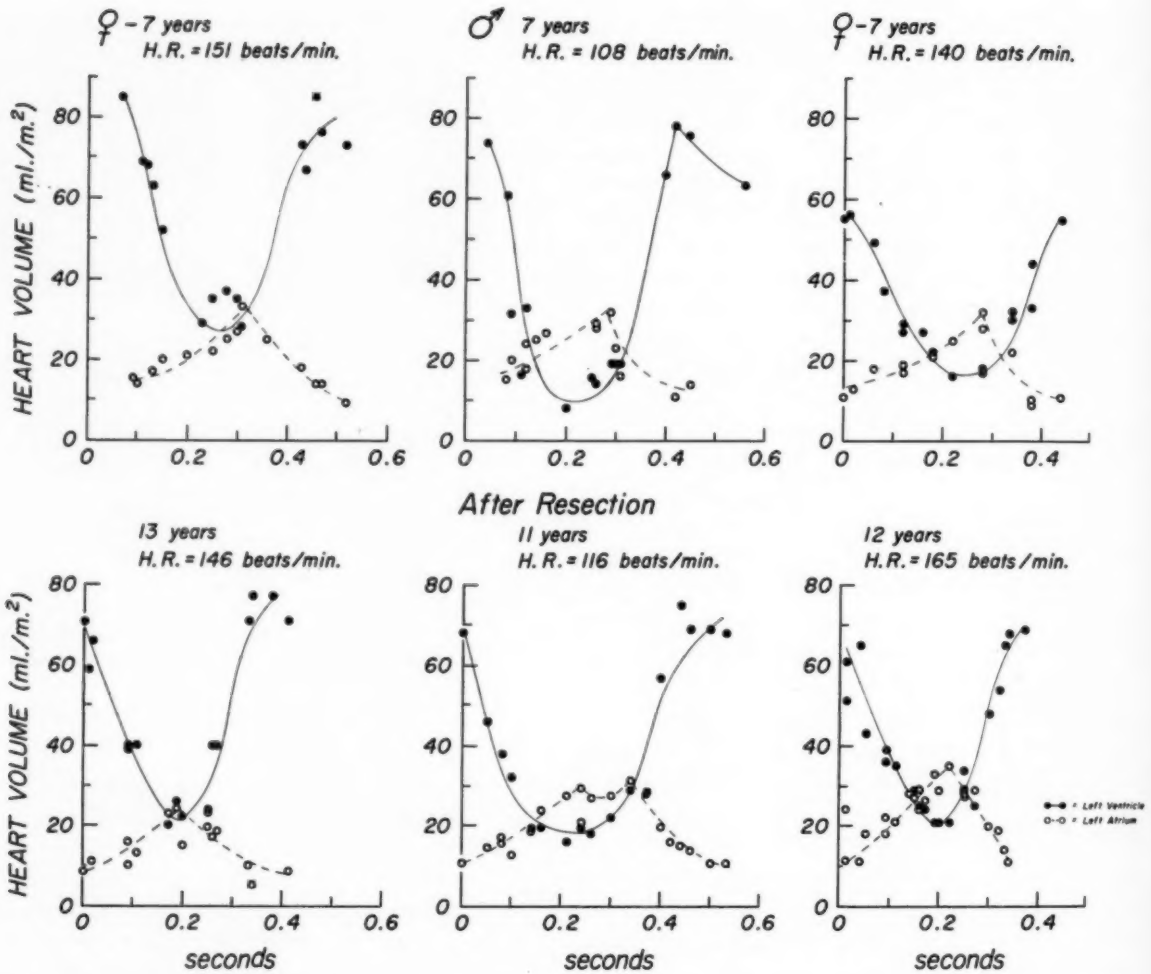

Fig. 4. Changing volumes (milliliters per square meter of body surface) of the left atrium and left ventricle preoperatively (*above*) and 4 to 5 years postoperatively (*below*) in Cases 1, 2, and 3. Note the general similarity in the magnitude and changes in volumes obtained in the paired studies.

postoperative studies are counted separately, our investigation affords 10 estimates of residual volume in the left ventricle. The values range from 10 to 30 ml./M.², averaging 29 per cent of the end-diastolic ventricular volume. This implies highly efficient ejection.

These results are in relatively good accord with the data that have been presented by Gribbe and associates.[3] These investigators, using cineangiocardiographic recordings from anesthetized dogs, calculated the average stroke volume to be 60 per cent of the end-diastolic volume, implying an average residual volume of 40 per cent. Their findings in nonanesthetized dogs were similar.

These end-systolic volumes are considerably lower than those reported by Chapman and associates[1] and by Holt.[5] In a cineangiocardiographic study of anesthetized dogs, Chapman's group found that the residual volume of the left ventricle averaged 51 per cent (range, 37 to 56 per cent) of the end-diastolic volume. Holt, using dye-dilution and electrical conductivity methods in dogs, reported that residual volumes averaged 54 per cent of end-diastolic values. Chapman and co-workers[2] had reported previously, however, a cineangiocardiographic study on one healthy human subject in whom they found the residual volume to be 15 per cent of the end-diastolic volume.

It is possible that the patients in our study had lighter anesthesia and better oxygenation of their tissues than did the anesthetized dog. These two factors may be of importance in obtaining low end-systolic values. Neither the contrast me-

dium nor the slightly elevated intrabronchial pressure (5 to 10 cm. of water) are thought to have affected greatly the left-heart volumes in our subjects. It is frequently observed, however, that the heart rate increases with the introduction of anesthesia. No further change in heart rate occurs during angiocardiography, although bradycardia may develop some while after the time of the left-heart opacification.

Left ventricular stroke volumes in our 10 studies ranged from 34 to 59 ml./M.^{2}. Such values are reasonable and are of the order of magnitude one might expect in normal subjects. However, the estimated cardiac indices were rather high. If 5.5 L./min./M.^{2} is taken as the upper limit of normal values for children, only four of the 10 were within the range of normal. The heart rates of the patients with the higher cardiac indices ranged from 108 to 186.

One patient, the last in Table I, had such a high heart rate that the frames (six exposures per second) happened to fall in only two phases of the cardiac cycle. All points clustered about the lines representing 0.04 and 0.20 second after the R wave, and hence no curve could be constructed, as was easily done in the other cases. This case illustrates the shortcomings of this method of estimation of volume when the heart rate is very rapid.

The changes of atrial volume, as estimated by this method, are remarkably reproducible, and when plottedt hey form a curve which is in many ways the inverse of that obtained from the ventricle. However, the magnitude of the change of atrial volume averages only one third that of ventricular volume. Arvidsson[6] has suggested the reason for this: namely, the atrium is a chamber closed only at one end for a relatively short time during any cardiac cycle, and, hence, during diastole the atrium does not expand because inflow and outflow occur simultaneously.

These findings indicate that the passage of the greater proportion of the stroke volume into the left ventricle is governed by factors other than atrial contraction. Indeed, the greatest change in atrial volume appeared to occur immediately after systole and not in presystole, although the rapid heart rates render such distinctions uncertain.

Effect of surgical repair. Three patients were studied before and up to 5 years after surgical repair of coarctation. Each repair was considered adequate by the surgeon, and comparison of preoperative and postoperative blood pressures in the arms and legs supports the surgeon's opinion. No significant changes were demonstrated in any of the parameters studied: left atrial end-systolic and end-diastolic volume, and left ventricular end-systolic and end-diastolic volume.

The fact that the preoperative and postoperative studies agreed closely suggests that left ventricular volumes were within the range of normal in these children before operation. A definitive opinion should await the results of simultaneous determination of the cardiac output according to established physiologic methods.

Summary

Arvidsson's method of estimating volumes of the left-heart chambers by angiocardiographic techniques has been found to be practical in application. The method has been applied in 10 studies of seven patients with compensated coarctation of the aorta. Left ventricular stroke volumes were found to average 46 ml./M.^{2} (range, 34 to 59), and the end-systolic volume in the left ventricle to average 19 ml./M.^{2} (range, 10 to 30). This evidence indicates that left ventricular ejection is highly efficient.

Changes in left atrial stroke volume were much less marked, averaging only 15 ml./M.^{2} (range, 10 to 21) during any cardiac cycle.

No significant differences in changes of left-heart volume were found in three patients who were studied both before and 4 to 5 years after surgical correction of the coarctation.

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Blood pressure measurements of urban Zulu adults

*N. Scotch, Ph.D.**
*B. Gampel, M.B., B.Ch., D.P.H.****
*J. H. Abramson, B.Sc., M.B., B.Ch.***
*C. Slome, M.B., Ch.B., D.P.H.****
Boston, Mass.

Various observers have differed widely in their reports on blood pressure measurements and the prevalence of hypertension among Africans. As Phillips and Burch[1] stated in a recent review article, "some reports show that native Africans have lower arterial blood pressure than Caucasians and that hypertension is rare in the Negro[2-7] whereas others report hypertension not to be rare in Native Africans but that it may even be more frequent than in Caucasians.[8-12]"

The present study was part of a larger project on nutrition and hypertension begun in 1958, by the Department of Social, Preventive and Family Medicine, University of Natal.

Subjects and method

The study was carried out in an African housing scheme occupied predominantly by Zulus (72.5 per cent). The persons examined comprised 382 adults (271 women and 111 men, aged 18 years or more), drawn from a randomly selected sample consisting of all the adult Zulu residents of every seventh home in the housing scheme. Of the initial sample, 76.6 per cent of the women and 45.2 per cent of the men were examined. The others could not be examined for a variety of reasons, so that there was some question as to how representative the sample was. Accordingly, visits were made to the homes of half of the persons who had not been examined in order to ascertain the reasons for their nonexamination and, more important, to see whether they differed from examined persons in their marital state, parity, social class, father's social class, income, food expenditure, education, and other variables. Since the few differences which were found were slight, or involved factors bearing no significant relationship to levels of blood pressure, it was concluded that the persons examined were fairly representative of the total Zulu population of the housing scheme. Men in the lowest social class (unskilled laborers), for example, were significantly underrepresented among the per-

From the Harvard School of Public Health, Boston, Mass., and the Department of Social, Preventive and Family Medicine, University of Natal, Durban, South Africa.
This work was supported in part by a supplementary grant (H 4197-SI) from the National Heart Institute, U. S. Public Health Service. Financial assistance was also received from the Russell Sage Foundation, Washington State University, and the Program of African Studies, Northwestern University.
Received for publication July 21, 1960.
*Harvard School of Public Health, Boston, Mass. Work done during the tenure of a Research Fellowship of the U. S. Public Health Service.
**Department of Social, Preventive and Family Medicine, University of Natal, Durban, South Africa.
***Present address: Hebrew University-Hadassah Medical School, Jerusalem, Israel.

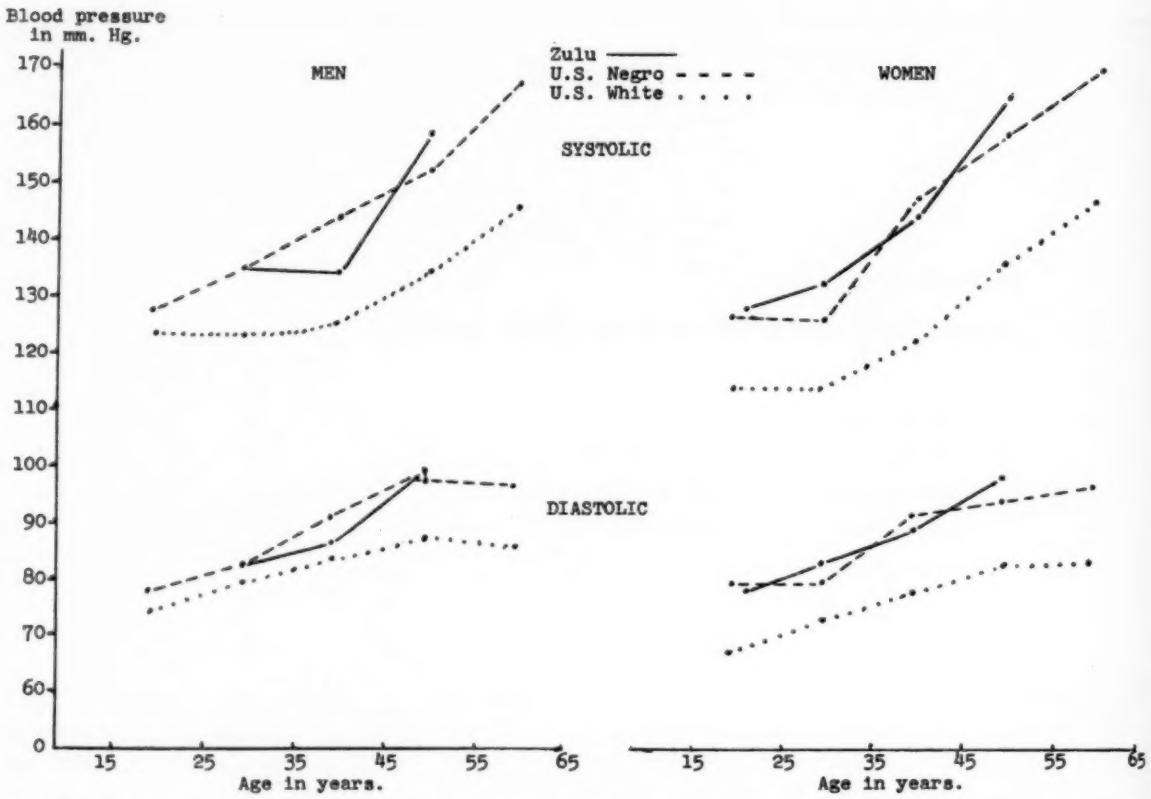

Fig. *1.* Mean systolic and diastolic blood pressures of Zulu adults, by sex and age. Comparison with Negro and white adults in the United States.[15] The values charted for Zulu adults are based on all available measurements for persons aged 18-64 (including pregnant women), excepting men aged 18-24 and 55-64, who numbered 14 and 8, respectively.

sons examined. Although social class was found to bear a significant relationship to the levels of blood pressure, standardization of the results in accordance with the social class structure of the total sample produced a negligible difference in the prevalence of hypertension.

Blood pressures were taken in the Institute of Family and Community Health, Durban, to which participants were transported from their homes. This Institute is adjacent to the housing scheme, for which it has provided a medical service for some years, and most of the subjects were familiar with it. All the readings were made by the same physician (C. S.), with the exception of three cases. Patients were seated, and the pressure was taken with a Baumanometer, the diastolic pressure being equated with the disappearance of the sound. In order to examine the variation of blood pressure in the two arms,[13] the initial reading of blood pressure was taken on the right in some cases, and on the left in others. For the purposes of the analysis which follows, the initial reading was used, regardless of whether it was taken on the left or the right side.

Two separate criteria were used in classifying persons as hypertensive, the first being more stringent: criterion *a*—a systolic pressure of over 160 mm. Hg, and/or a diastolic pressure of over 96 mm. Hg; criterion *b*—a systolic pressure of 140 mm. Hg or more, and/or a diastolic pressure of 90 mm. Hg or more.

The sample included 5 persons with congestive cardiac failure, all ambulant; 4 of them were hypertensive.

Results

The levels of mean and median blood pressure of our subjects are set out in Table I, and the prevalance of hypertension, using the two separate criteria explained above, is shown in Table II.

Studies of hypertensive women of the United States,[14] and of African women,[11] have indicated that blood pressures tend to drop in pregnancy. This was confirmed

in our subjects. Of the 31 pregnant women who were 20 to 34 years of age, none were hypertensive by criterion *a*, and 16.1 per cent by criterion *b*. Of the other 108 women in this age group, 19.4 per cent were hypertensive by criterion *a*, and 38.9 per cent by criterion *b*. The difference was significant ($p < .01$ using criterion *a*, and $< .05$ using criterion *b*). The mean ages of the pregnant and nonpregnant women were similar: 31.5 and 30.4 years, respectively. In view of this finding, separate figures for nonpregnant women are given in Table I, and data relating to pregnant women are not included in the analysis of the prevalence of hypertension (Table II).

Table I. *Blood pressure (mm. Hg) of Durban Zulu adults, by sex and age. Medians, means, and standard deviations*

Sex, and age (yr.)	*Number*	*Systolic pressure*			*Diastolic pressure*		
		Median	*Mean*	*Standard deviation*	*Median*	*Mean*	*Standard deviation*
Men:							
18–24	14	139	136	—	84	81	—
25–34	34	138	133	17.25	80	81	13.65
35–44	32	131	133	18.14	84	84	10.57
45–64	22	156	157	26.18	95	98	12.19
65 and over	9	170	171	—	90	90	—
	111						
Women:							
18–24							
Total group	56	128	127	16.46	78	77	15.95
Nonpregnant women	45	129	129	15.82	79	80	20.15
25–34							
Total group	100	128	131	20.35	80	82	16.06
Nonpregnant women	80	130	134	16.94	84	84	25.15
35–44*	59	143	144	28.10	90	88	14.44
45–64*	45	160	165	28.57	100	98	15.04
65 and over*	11	173	163	—	88	87	—
	271						

*There were no pregnant women in these age groups.
Standard deviations are not given for groups which contained fewer than 20 persons.

Table II. *Prevalence per cent of hypertension,* by sex and age*

Age (yr.)	*Percentage with hypertension*					
	Men			*Women*		
	Number	*Criterion a*	*Criterion b*	*Number*	*Criterion a*	*Criterion b*
18–24	14	28.6	50.0	45	6.7§	31.1
25–34	34	17.6	50.0	80	23.8	42.5‡
35–44	32	15.6†	43.8†	59	35.6†	64.4
45 or over	31	58.1	80.6	56	62.5	75.0
45–54	15	60.0	80.0	25	60.0	72.0
55–64	7	57.1	71.4	20	65.0	80.0
65 or over	9	55.6	88.9	11	63.6	72.7

*As defined by the two criteria explained in the text.
†$p > .01$
‡$p > .02$
§$p > .05$
Pregnant women were excluded from this analysis.

In both sexes, levels of mean blood pressure and the prevalence of hypertension rose with age. This increase becomes apparent after the age of 44 in men, but sooner in women (Tables I and II). This earlier rise in women was reflected in the finding that in the 35-44-year age group the women had a higher mean and median systolic blood pressure and a greater prevalence of hypertension than did the men. The difference in mean systolic pressures is statistically significant ($p < .05$).

The mean systolic and diastolic pressures of our subjects are shown graphically in Fig. 1, by age and sex, together with comparative figures for population samples of Negro and white persons in Georgia, U.S.A.[15]

Discussion

It is apparent from Fig. 1 that our subjects tend to have mean pressures similar to those of Negroes of the United States, who are recognized as having a high prevalence of hypertension,[1] and higher mean pressures than those of whites of the United States. Excepting the diastolic pressures of men who are 25 to 44 years of age, the mean pressures are closer to those of the Negro group cited than to those of the white group.

The conclusion that this urban Zulu group shows a relatively high prevalence of hypertension is supported by data on a similar group of Zulus living in a rural native reserve. In general, the urban Zulus have a significantly higher incidence of hypertension and significantly higher blood pressure values.[16]

The evidence suggesting an earlier rise in blood pressure in women than in men is consistent with Schrire's findings among Coloured hospital patients in Cape Town,[17] and those of Fraser among Coloured and African hospital patients in Johannesburg.[18]

Summary

A study of a population sample of urban Zulu adults in Durban, South Africa, revealed a high prevalence of hypertension. Mean blood pressures tended to be similar to those of Negroes of the United States and higher than those of whites of the United States.

In both sexes, levels of mean blood pressure rose with age; this rise appeared earlier in women than in men.

We wish to acknowledge the guidance and support of Professor M. J. Herskovits, Chairman, and the Program of African Studies, Northwestern University, Evanton, Ill. Also, we are indebted to Nursing Sisters C. C. Majola and T. Triegaardt, Medical Recorders W. H. Pietersen, S. J. Maharaj, and other members of the staff of the Institute of Family and Community Health, Durban. Thanks are due to Nino Mndlazi, who acted as interpreter and interviewer, and to Mrs. K. M. Wolfson for preparing the chart for Fig. 1. Mr. Roderick Sprague of Washington State University contributed his services as statistician.

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Heart murmurs simulated by arterial bruits in the neck

John F. Stapleton, M.D.
Muhsin M. El-Hajj, M.D.
Worcester, Mass.

The proper assessment of systolic murmurs in children is a common problem in all cardiac clinics. Although physicians are now generally alert to the frequency of physiologic murmurs in children, many such murmurs, nevertheless, fall into the borderline category and are referred for further cardiac evaluation.

This communication reviews one uncommon type of physiologic murmur in children, in which a systolic arterial bruit arising in the lower neck is transmitted to the base of the heart and recorded during routine physical examination as an aortic and/or pulmonic systolic murmur. In some instances the bruit comprises most or all of the basal murmur; in other cases the bruit augments an innocent cardiac murmur so that Grade 3 or more intensity results from the dual source of sound.

Four patients with supraclavicular bruits are reported herein who presented basal systolic murmurs which could be well heard along the upper sternal borders. In Cases 1 and 2, transmission was prominent enough to the right of the sternum that an aortic ejection murmur was simulated. In Cases 3 and 4, the maximum intensity of the transmitted bruit was along the left sternal border, simulating a pulmonary ejection murmur. The illustrated phonocardiograms were recorded with Sanborn Twin-Beam or Stethocardiette phonocardiograph at a paper speed of 75 mm. per second. The microphone was held by the hand over the neck, with just enough pressure to provide good contact with the surface of the skin.

Case reports

Case 1. A 7-year-old asymptomatic boy was referred to the rheumatic fever clinic for evaluation of a cardiac murmur which was known to have been present since he was 3 years old. Penicillin prophylaxis had been started when this murmur was discovered, and had been discontinued only recently. Frequent syncopal episodes which were found to be petit mal were controlled with medication. There was no history of rheumatic fever. Family and past medical histories were normal. Examination disclosed a Grade 3 ejection type of systolic murmur which was heard best in the pulmonic area but also along the mid left sternal border and in the aortic area (Fig. 1). Prominence of the aortic murmur was, in particular, the auscultatory feature which raised the question of aortic stenosis. Inching the stethoscope up the sternal borders revealed loud, bilateral supraclavicular bruits. A physiologic third sound and venous hum were prominent. The ECG and chest x-ray film were normal.

Case 2. A 9-year-old Negro boy was admitted to the hospital with acute glomerulonephritis. An aortic ejection type of systolic murmur was discovered as an incidental finding on physical examination, and was regarded as indicating aortic stenosis until the significance of his loud right supraclavicular bruit was appreciated (Fig. 2). The ECG and chest x-ray film were normal.

Case 3. A 14-year-old asymptomatic school boy was referred for evaluation of a cardiac murmur. Systemic review and past medical and family histories were normal. Examination disclosed a tall, asthenic, white boy with slight pigeon breast and prominent point of maximal impulse. A Grade 3 systolic murmur was present in the pulmonary area, with transmission down the left sternal border to the apex. Inching the stethoscope up the left sternal

From the Department of Medicine, St. Vincent Hospital, Worcester, Mass.
Received for publication July 22, 1960.

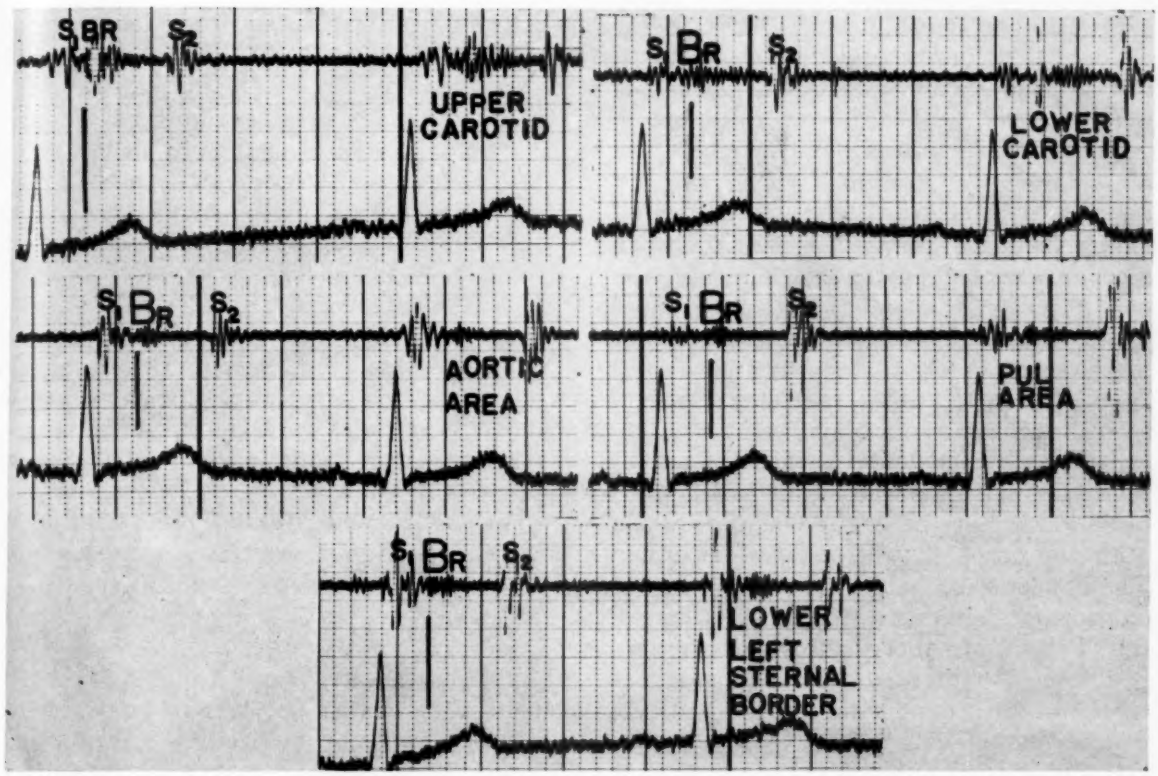

Fig. *1.* Asymptomatic 7-year-old boy with prominent basal systolic murmurs which correspond to louder supraclavicular bruits.

border from the pulmonic area disclosed that the murmur progressively increased, reaching its peak intensity just above the medial clavicle on both sides (Fig. 3). A venous hum and prominent physiologic third sound were present. The ECG and chest x-ray film were normal.

Case 4. A 17-year-old white asymptomatic x-ray technician was referred for evaluation of a cardiac murmur. Past medical and family histories were normal. A Grade 3 ejection type of systolic murmur was evident in the pulmonic area, and was also heard in the aortic area and at the apex. Inching the stethoscope up the sternal borders disclosed loud supraclavicular bruits bilaterally (Fig. 4). Examination also disclosed a thrusting point of maximal impulse, prominent physiologic third sound, and venous hum. The ECG and chest x-ray film were normal.

Discussion

The bruit is characteristically abrupt, occupying, in all, no more than a third of systole. The onset is later than that of basal ejection murmurs, commencing usually 0.12 to 0.16 second after the onset of QRS. It exhibits a diamond-shaped contour, with swift development of Grade 3 to 4 peak intensity and prompt decline around mid-systole. Such a contour classifies the murmur as ejection in type; the early onset and brief duration suggest a flow rather than obstruction mechanism. It is best heard immediately above the clavicle(s), and fades out rapidly as the stethoscope is inched along the common carotid or subclavian arteries. It is less well heard below the clavicles, and ordinarily makes insignificant contribution to the basal cardiac sounds. However, as illustrated here, bruits of exaggerated intensity may be transmitted to the aortic or pulmonic regions. The murmurs are sometimes bilateral but tend to predominate on one side or the other. Carotid or subclavian compression has no significant effect; likewise, no change occurs with various postural maneuvers.

Edwards and Levine[1] have called attention to the impact sound in early systole which precedes a crescendo-decrescendo bruit when an artery is partially compressed. This sound is clearly identified in Figs. 2, 3, and 5; indeed, on superficial inspection the impact sound could be mistaken for the first heart sound.

The mechanism of these bruits is speculative. Obstruction is a well-known cause of murmurs over vessels. Mild narrowing

causes a short systolic bruit; more severe degrees of occlusion prolong this murmur, so that in marked obstruction a continuous murmur may be heard over the stenotic segment.[2-4] The bruits described here are all short, early systolic, indicating that any obstruction present is probably mild. The other features of hypercirculation which are present (thrusting point of maximal impulse, prominent ventricular rapid filling sound, venous hum) suggest a flow mechanism. Possibly these murmurs arise from the aortic arch, where streams of blood enter the great branches at high velocity. The great-vessel orifices might be relatively narrow in early systole, when large increments of flow develop abruptly after the onset of ventricular contraction. The impact sound which is sometimes present suggests sudden distention of the vessels. Failure of subclavian or carotid compression to obliterate these bruits points to an origin proximal to the cervical segments of these vessels. Since the subjects were healthy, young persons, a physiologic origin appears likely; since angiographic studies were not justified, etiological considerations are necessarily tentative.

That these bruits arise from the proximal segments of branches of the aortic arch was strongly suggested by the findings in a 48-year-old man who was admitted because of recent dysarthria and hemihyperesthesia. Examination disclosed a loud systolic bruit in the right, medial supraclavicular region (Fig. 5) which was identical in timing and location to the bruits described above in young, healthy individuals. This murmur could be readily followed down to the aortic area, where it simulated an aortic ejection murmur. Like the physiologic bruits it faded out rapidly when the stethoscope was inched up the common carotid, and was not significantly altered by subclavian or carotid compression. Because of hypertension in the right upper extremity and hypotension in the left upper extremity, as well as the bruit, the aortic arch was explored. A prominent thrill was palpated over a narrowed, sclerotic, proximal innominate artery. The degree of obstruction was not severe, and surgical intervention was withheld. Thromboendarterectomy was performed on a severely narrowed proximal left subclavian artery.

That cervical bruits transmit to the pre-

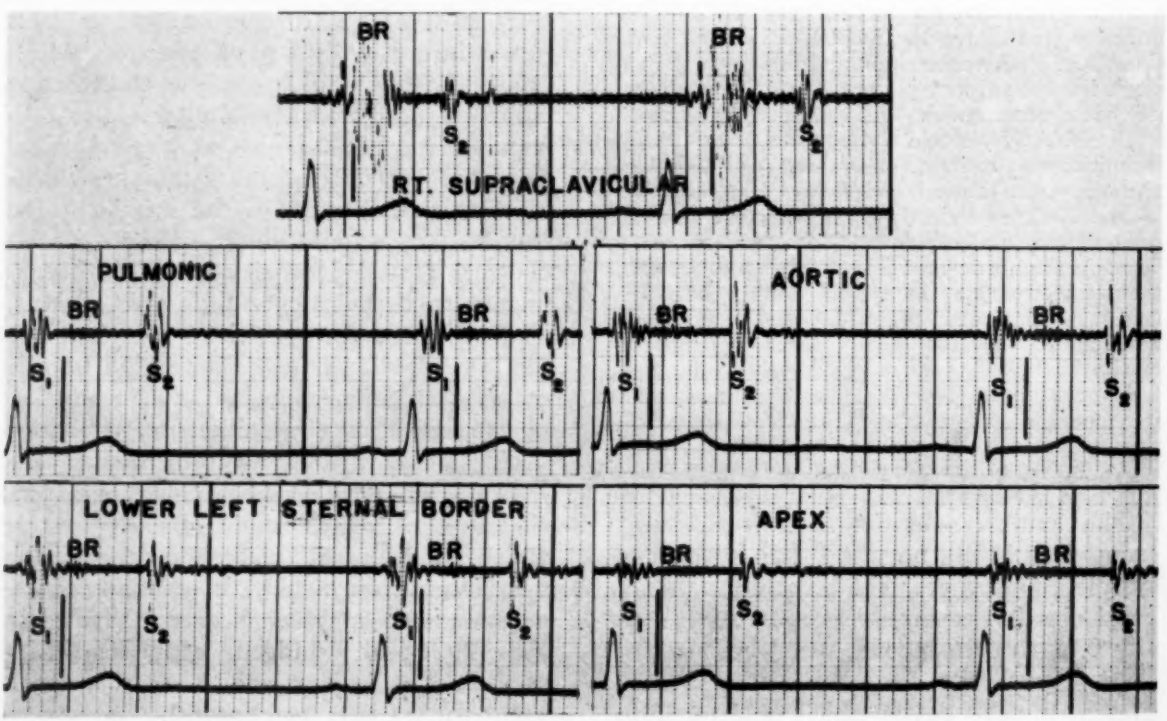

Fig. 2. Nine-year-old Negro with acute glomerulonephritis. Loud right supraclavicular bruit (*BR*) transmits to base of heart, simulating aortic stenosis. Normal ECG and x-ray film. Note impact sound (|) in supraclavicular region.

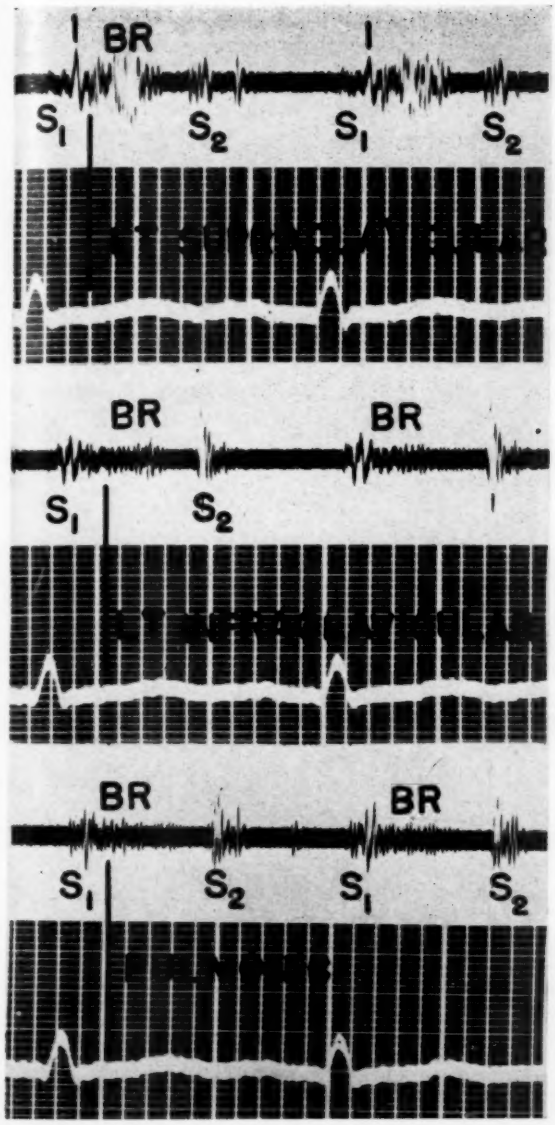

Fig. *3.* Fourteen-year-old asymptomatic boy with Grade 3 pulmonic systolic murmur derived from loud supraclavicular bruit (*BR*). Note impact sound (|) in supraclavicular region.

cordium has been previously emphasized by Cassels,[5] Levine and Harvey,[6] and others. Similarly confusing transmission of venous hums has also been described.[5] It is not possible to state the relative frequency of this mechanism of functional basal cardiac murmurs as compared to true aortic and pulmonic ejection murmurs. It is our impression that, although the majority of physiologic basal murmurs are not on this basis, cervical bruits will be found to occasionally contribute to such murmurs if auscultation of the neck is regularly practiced. Since bruits arise from the compression of normal vessels, vascular auscultation should be done gently so as not to create external pressure with the stethoscope piece.

Occasionally, the murmur of aortic stenosis is loudest in the supraclavicular region. These instances occur in older patients with emphysema or other thoracic deformities and are not found in the young patient with normal lungs and chest structure. Thus, this differentiation has not been a factor in the patients discussed (Fig. 6).

The clinical significance of this phenomenon lies in the fact that all patients reported upon here were referred because of the possibility that they had heart disease. Indeed, one patient was examined several times in a cardiac clinic before supraclavicular auscultation disclosed the basis of his murmur. Aortic systolic mur-

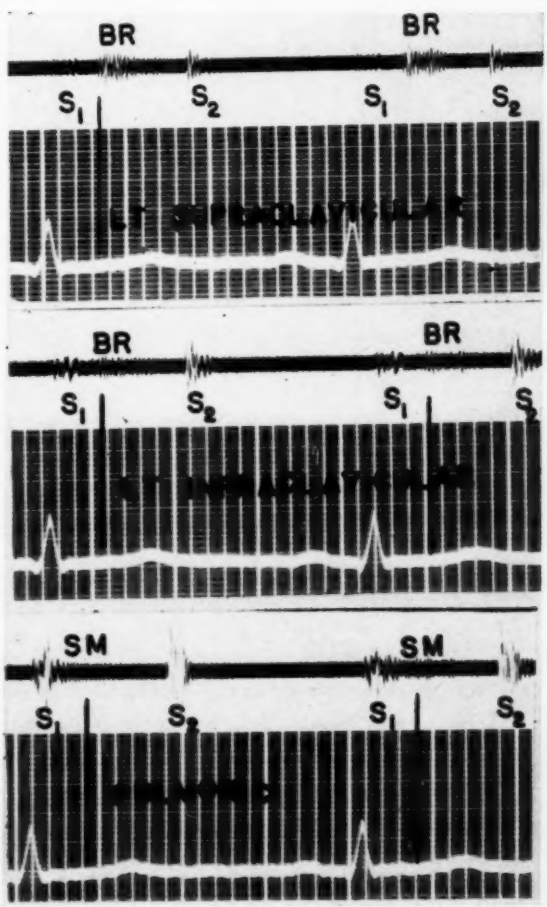

Fig. *4.* Seventeen-year-old girl with Grade 3 pulmonic systolic murmur. Loud supraclavicular bruit transmitted down sternal border to area of fusion with early systolic pulmonic murmur. Grade 3 intensity attributed to dual source of murmur.

murs are less frequently encountered in children than are murmurs to the left of the sternum. Thus, an aortic systolic ejection murmur in the intensity range of Grade 2 to 3 seriously raises the question of aortic stenosis. This lesion, when mild, may be manifested solely by such a murmur. Since left heart catheterization in the child is a formidable and sometimes inconclusive undertaking, the cause of such murmurs is often left undetermined rather than attempt this procedure. In like fashion, Grade 2 to 3 pulmonary systolic murmurs, in the absence of other findings, are often of uncertain explanation. Catheterization and angiocardiography are considered not to be justified for these borderline murmurs when the remaining clinical data are benign. Transmitted arterial bruit should be considered in all young patients who present a prominent basal systolic murmur without other evidence of heart disease. Other evidences of rapid circulation and slender chest configuration should increase suspicion.

Summary

1. A systolic, ejection type of bruit is sometimes heard in the medial supraclavicular regions of healthy young persons.

2. This bruit, when prominent, may transmit to the basal region of the heart and either simulate a systolic murmur or augment one already present.

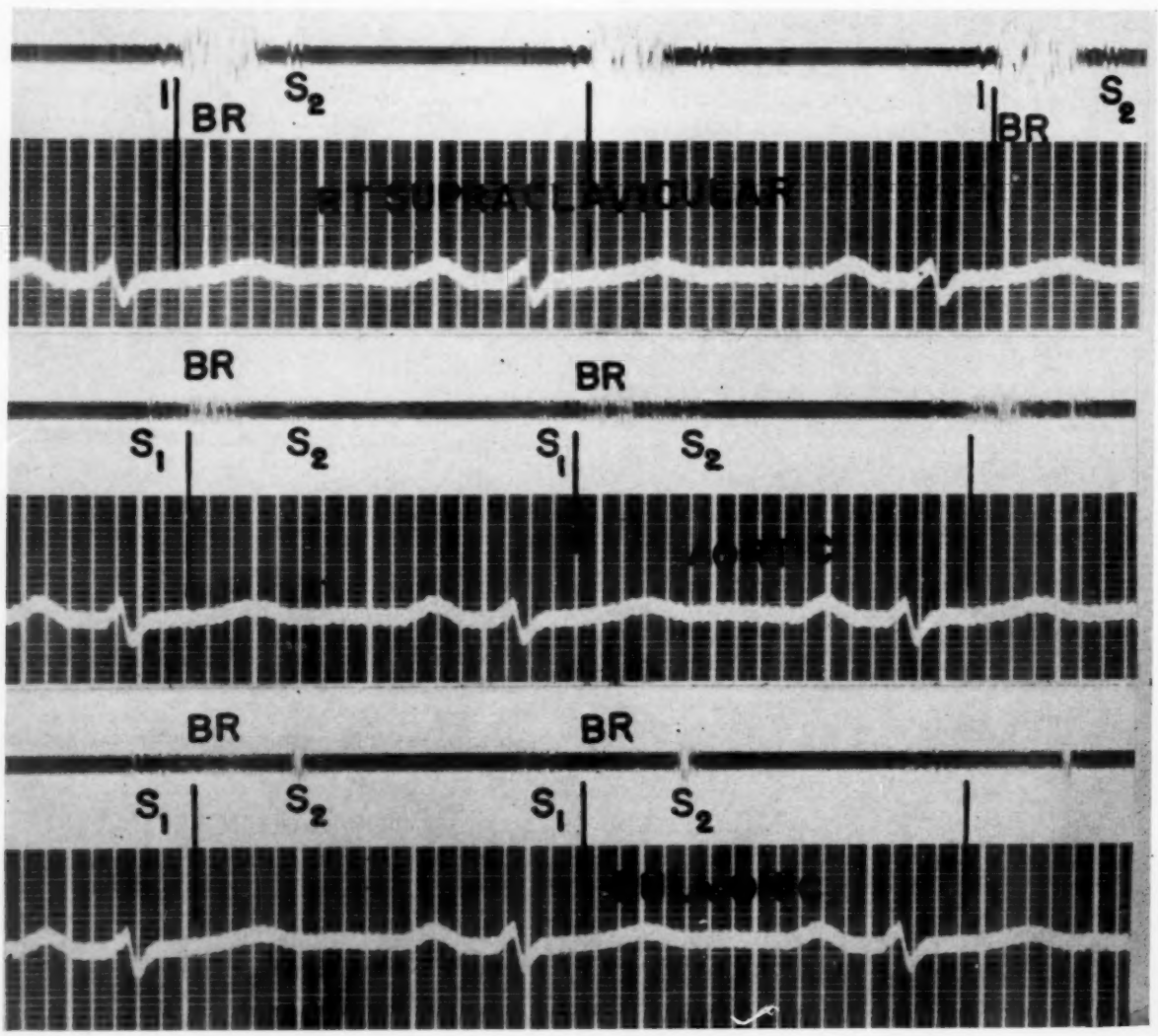

Fig. 5. Forty-eight-year-old man with right supraclavicular bruit (*BR*) which transmits well to the aortic area and fades out in the pulmonic area. Atherosclerotic narrowing and thrill at innominate artery orifice demonstrated by operation. Note impact sound (|).

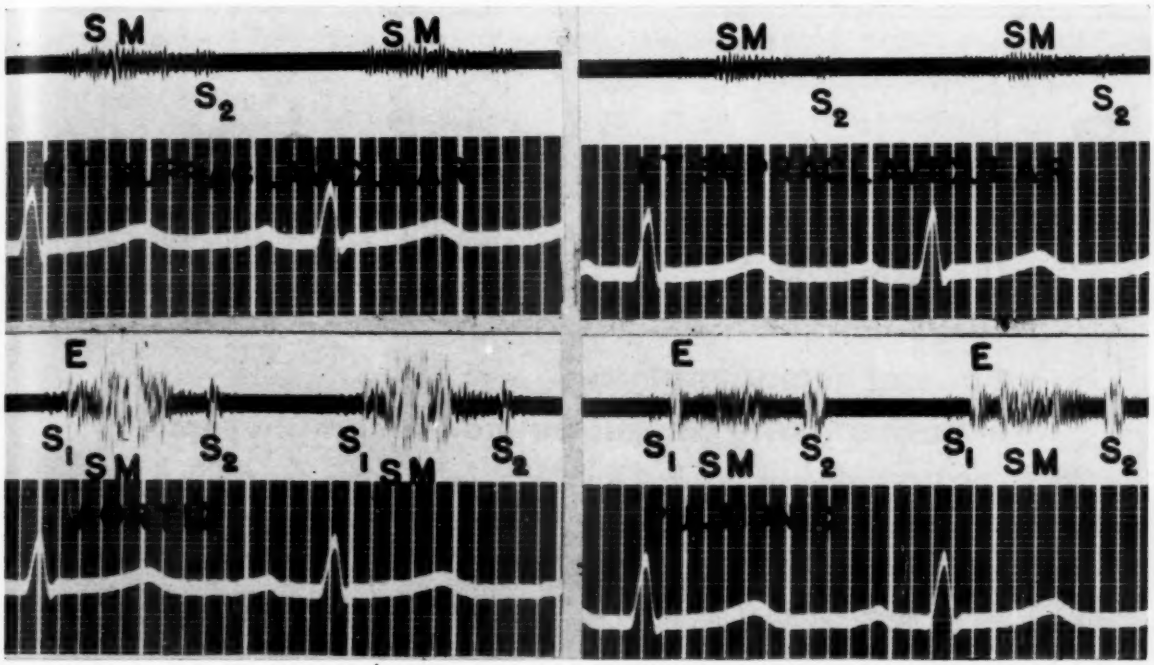

Fig. *6*. Five-year-old girl with congenital aortic stenosis. Note that the loud aortic murmur is softer in the supraclavicular region in contrast to the bruits illustrated. Recordings were made with the same volume setting in each region. *E*, Aortic ejection sound.

3. At times, the systolic murmur so produced may be Grade 3 in intensity and simulate an organic murmur.

4. Persons who exhibit this phenomenon are often of slender body build and have ventricular rapid filling sounds, vigorous apical impulse, and venous hum.

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The effects of "dry" heat on the circulation of man
General hemodynamics in patients with chronic pulmonary emphysema

Elmerice Traks, M.D.
Salvatore M. Sancetta, M.D.
Cleveland, Ohio

Data presented by us in a previous report[10] delineated the general hemodynamic effects of the exposure of resting patients with enlarged left ventricles, compensated and in failure, to a "dry" ambient environment of 98° ± 1 and 40 per cent humidity ±3 for a period of 2 hours. This exposure resulted in a significant fall in the pressures of the pulmonary and peripheral arterial beds, with a decrease in the respectively calculated resistances; no change occurred in the oxygen consumption and the cardiac output. The calculated work of the left ventricle decreased. It was speculated that the short-term exposure to a warm, *dry* environment was not deleterious to these patients, although Burch[5] has repeatedly emphasized the ill effects of a *hot and humid* environment upon such individuals.

It is a common clinical observation that people suffering from chronic pulmonary disease are also poorly tolerant of hot and humid weather. Contrariwise, it appears important to know whether these people tolerate a warm and dry environment, at least in the resting state and for a brief period of time, as well as people with a diseased left ventricle[10,11] would appear to do. The current report presents the data gathered in 10 patients with chronic pulmonary emphysema who were subjected for 2 hours to an ambient temperature of 98° F. and a humidity of 40 per cent.

Materials and methods

Ten male patients who ranged in age from 39 to 63 years were studied. All had chronic pulmonary emphysema of varying severity, as gauged in all instances by a decreased total vital capacity, a reduction of the first second expiration time to less than 60 per cent, and increases in the total lung volume and residual functional volume to levels above 40 per cent of the predicted normal values. None of the patients had a demonstrably diseased left ventricle, and all were normotensive.

The details of procedure were identical to those previously reported for the patients with diseased left ventricles.[10] All studies were performed in the postabsorptive state, but in most instances small doses of chloral hydrate rather than a barbiturate were employed for sedation. After right-sided cardiac catheterization,

With the technical assistance of Gladys Heckman, R.N., Hanna Janouskovec, R.N., and Helen Haney, A.B.
From the Department of Medicine, Cleveland Metropolitan General Hospital, and Western Reserve University, Cleveland, Ohio.
Supported by U. S. Public Health Service Grant No. H-4302, and carried out during the tenure of a Research Fellowship from the American Heart Association (Dr. Traks).
Received for publication Aug. 19, 1960.

Table I. *Individual data for 10 subjects with chronic pulmonary emphysema (control levels and changes after 2-hour exposure to ambient temperature of 98° ± 1° F.)*

Patient—Race, Sex, Age, Body Surface			P_{RA_m}	P_{RV_m}	P_{PA}	P_{BA}	*HR*	*Vent./M.²*	$BMRO_2/M.^2$	*A. V. D.*	*C. I.*	pCO_2	*RVWk.*	*Pu. TR*	*ETPR*	*Peripheral arterial saturation (%)*
C. A.	W, M	C	(3.7)	(9.6)	17/11 (13)	116/69 (89)	65	4.42	96	4.99	1.93	34	1.62	336	2,301	90.2
62	1.60	2	(3.8)	(9.8)	18/11 (14)	102/65 (79)	83	5.53	130	5.44	2.39	26	2.05	293	1,652	89.8
J. B.	W, M	C	(2.3)	(12.1)	31/12 (19)	112/67 (84)	73	4.25	104	5.48	1.91	39	2.67	482	2,100	90.4
63	1.67	2	(2.2)	(12.3)	29/14 (19)	98/55 (69)	75	4.38	110	5.65	1.90	43	2.74	477	1,689	89.7
J. McC.	W, M	C	(− .4)	(14.2)	37/21 (28)	103/75 (88)	93	3.70	88	6.93	1.27	39	2.65	1,198	3,763	93.2
59	1.47	2	(− .9)	(14.1)	34/21 (27)	92/70 (82)	101	3.99	107	7.64	1.39	40	2.83	1,056	3,208	94.4
C. T.	W, M	C	(5.7)	(18.2)	43/16 (27)	131/78 (100)	79	3.90	130	4.83	2.70	45	4.82	395	1,463	87.3
51	2.03	2	(5.0)	(20.1)	40/21 (30)	123/72 (91)	86	4.59	131	4.70	2.80	43	6.04	421	1,283	86.7
E. S.	W, M	C	(4.6)	(26.2)	32/17 (24)	115/77 (96)	69	3.31	103	4.54	2.28	52	7.03	498	1,992	88.1
49	1.69	2	(4.5)	(27.1)	31/18 (24)	111/74 (90)	74	4.40	126	4.36	2.87	46	7.32	396	1,484	86.5
J. D.	N, M	C	(3.0)	(11.5)	29/13 (19)	106/72 (82)	67	6.85	85	5.00	1.70	45	2.06	492	2,185	92.5
44	1.82	2	(−2.0)	(5.2)	23/10 (15)	80/54 (63)	75	8.20	111	5.31	2.10	37	2.16	313	1,315	91.4
H. E.	N, M	C	(1.0)	(19.0)	57/29 (34)	154/80 (104)	68	2.76	97	4.54	2.16	56	5.55	678	2,074	89.4
39	1.86	2	(1.4)	(18.0)	54/23 (32)	127/78 (90)	70	3.02	130	4.78	2.71	52	6.42	507	1,427	88.7
G. G.	N, M	C	(5.7)	(14.4)	33/14 (21)	113/75 (86)	108	2.79	75	4.81	1.56	46	1.94	642	2,580	91.4
50	1.71	2	(5.1)	(13.5)	30/13 (19)	88/62 (69)	136	3.52	106	5.32	2.00	44	2.40	444	1,612	90.3
J. G.	N, M	C	(7.5)	(25.1)	60/32 (41)	151/81 (98)	94	3.90	117	5.97	1.97	37	4.95	1,040	2,486	90.6
58	1.60	2	(4.7)	(20.2)	55/27 (38)	120/60 (79)	100	4.09	137	5.81	2.37	40	5.24	801	1,665	88.4
W. J.	N, M	C	(4.8)	(21.0)	55/23 (37)	112/69 (83)	97	3.79	128	4.24	3.03	42	7.01	534	1,206	68.4
52	1.82	2	(4.9)	(21.4)	53/24 (36)	100/63 (73)	106	4.53	140	4.46	3.15	43	7.42	503	1,017	76.4

P_{RA_m}, P_{RV_m}, P_{PA}, P_{BA} = Right atrial, ventricular, pulmonary, and brachial arterial pressures (mean pressures in parentheses). HR = Heart rate. Vent./M.² = Minute ventilation in L./M.²/min. $BMRO_2/M.^2$ = Oxygen consumption in c.c./M.²/min. A. V. D. = Arteriovenous oxygen difference in volumes per cent. C. I. = Cardiac index in L./M.²/min. pCO_2 = Arterial tension carbon dioxide. RVWk. = Right ventricular work in kilogram-meters/min. Pu. TR and ETPR = "Total pulmonary resistance" and systemic vascular resistance in c. g. s. dyne cm.$^{-5}$ units. C = Control. 2 = "Two-hour" heat data. (The 1-hour "heat" data are omitted; please see text.)

Table II. *Average and percentile changes, control and "2-hour" heat data; statistical analyses*

	P_{PA}	P_{BA}	*Heart rate*	*Vent./M.²*	$BMRO_2/M.^2$
C	39/19 (26)	121/74 (91)	81	3.97	102
2	37/18 (25)	104/65 (78)	90	4.63	123
%	−3.8	−14.3	+11.1	+16.6	+20.6
"P" = C $\overline{vs}$ 2	<.2>.1	<.001	<.02>.01	<.005 >.001	<.001
"P" = Change in group $\overline{vs}$ changes in patients with enlarged left ventricles (see below)*	<.005 >.001	<.05>.02	<.6>.5	<.3>.2	<.1>.05

*The changes induced by a 2-hour exposure to heat are compared to changes induced in a group of patients with enlarged left ventricles Fisher's "t" test for groups less than thirty.

control data were obtained at the comfortable environment of 73° F. and 40 per cent humidity, and again 1 and 2 hours after exposure to an ambient temperature of 98°F.

Systemic vascular resistance and "total" pulmonary vascular resistance* were calculated according to standard formulas.[8] The "work" of the right ventricle was calculated as follows[9]:

$$RVw = \frac{PFx\ (RVm - RAm) \times 13.6 \times 1.05}{1,000} = Kg.M./min./M.^2$$

where RVw = work of right ventricle against pressure; PF = pulmonary flow, liters/min./M.²; RVm = right ventricular mean pressure, mm. Hg; RAm = right atrial mean pressure, mm. Hg; 13.6 = specific gravity of Hg; 1.05 = specific gravity of blood.

The normal range for "work" by the right ventricle with the patient at rest is considered to be 0.5 to 1.1 Kg.M./min./M.².

The "work" of the left ventricle was likewise calculated by a standard formula.[9]

*This value is intended to express the composite of resistances offered to the right ventricle by the pulmonary blood vessels, the mitral valve, and the left ventricle in diastole. As such, it is believed to be a useful qualitative indicator of the predominant directional change in this circuit.

Results

Individual data are presented in Table I. Values obtained at the end of 1 hour of exposure to heat are omitted, since they did not differ greatly from those gathered at the end of the 2-hour period. Certain other noncontributory data, though mentioned in the text, are not tabulated. Averages, percentile changes, and significance analyses are presented in Table II.

The changes noted in these patients are also compared to those previously reported for patients with a diseased left ventricle[10]; this comparison analysis is included in Table II.

All patients except one (C.A.) had pulmonary hypertension, and one subject (J.G.) was in mild right ventricular failure. The pulmonary wedge pressure was normal in each instance.

There was no change in the pulmonary arterial pressure during exposure to the warm environment. The brachial arterial pressure decreased in all subjects. The heart rate increased. The control average respiratory rate was 21 and did not change (data omitted). Cheyne-Stokes respirations were not noted at any time. Significant

A. V. D.	*Cardiac index*	*pCO_2*	*RVWk.*	*Pu.TR*	*ETPR*	*Peripheral arterial saturation (%)*
5.13	2.05	43.5	4.03	629	2,215	88.1
5.35	2.37	41.4	4.46	521	1,635	88.2
+4.3	+15.6	−4.8	+10.7	−17.2	−26.6	+0.1
<.05>.02	<.001	<.2>.1	<.02>.01	<.02>.01	<.001	<.9
<.005 >.001	<.005 >.001	<.1>.05	—	<.05>.02	<.3>.2	<.9

who were reported upon previously (Am. Heart J. 56:212, 1958).

increases were noted in the minute ventilation, the oxygen consumption, the arteriovenous oxygen difference, and the cardiac index. The calculated work of the right ventricle was greater than 1.1 Kg.M./min./M.^{2} during the control period in all patients, and increased significantly after the patients were exposed to the warm environment. The calculated left ventricular work decreased (data omitted). The average rectal temperature increased by 1.6°F. (data omitted). This was the same as that for the previously reported group of patients with enlarged left ventricles.[10] The calculated resistances decreased. There was some decrease in arterial pCO_2, although this was not significant. The peripheral arterial oxygen saturation was initially below normal in all patients and showed no significant change.

Discussion

The most important differences noted in these patients with pulmonary emphysema, when compared to the ones previously reported, are as follows: (1) The pulmonary arterial pressure did not change, in contrast to the significant decrease in the subjects with enlarged left ventricles. (2) The cardiac index increased. As a result, the "total" pulmonary resistance decreased, but did so significantly less than in the previous patients. (3) Most important of all, there was a significant increase in the calculated work of the right ventricle, whereas that of the left ventricle decreased. This is in marked contrast to the significant decrease in the calculated work of *both ventricles* in the previously reported patients, and implies at least a relative lack of reactivity of the pulmonary vascular bed to the stimulus of heat in the emphysematous subjects.

It was noted that the minute ventilation and the oxygen consumption increased in the emphysematous patients, although this was not sufficient in magnitude to differ significantly from the response of the patients with enlarged left ventricles, in whom no change was recorded. The increase in minute ventilation was due only to the increase in the depth of respiration. The reason for this increase in the ventilation is obscure. Burch has demonstrated that in resting normal subjects, as well as in those with left ventricular congestive heart failure, the amount of pulmonary ventilation is increased,[4] but the rates of loss of water and heat from the skin are decreased when these individuals are exposed to a *hot and humid* environment.[3] This places an undue stress particularly on the cardiovascular system of the patient with congestive failure.[1,7] Although a "dry"

heat does not appear to affect similarly such individuals, it is obvious that patients with emphysema are harmed even by this situation. One wonders then whether in these emphysematous individuals, with impaired alveolar ventilation and "puddling" of warm air in the lungs, a stimulus may not be provided which would favor loss of heat through the respiratory tract by increasing respiration and the excretion of carbon dioxide.[2] The increased metabolic rate might represent in good measure a response to the increased work of respiration; these patients were not made irritable by the hot and dry atmosphere, and, indeed, most of them dozed or slept quietly after the room temperature was elevated.

The data strongly suggest that hot weather, even though arid, is deleterious to patients with pulmonary emphysema, and that the more severely ill ones should be placed in an air-conditioned environment. This in no way suggests preferential treatment for these patients, when hospitalized, and when air-conditioning facilities are limited, over those with congestive heart failure due to a diseased left ventricle, since the therapeutic value of cool, dry air for the latter group of patients has been well established.[6]

Summary

After right-sided cardiac catheterization, 10 resting male patients with chronic obstructive pulmonary emphysema were exposed to an ambient temperature of 98°F. and a comfortable humidity of 40 per cent for 2 hours. Restlessness and increased motor activity did not occur.

Whereas the brachial arterial pressure decreased significantly, the pulmonary arterial pressure did not change. The minute ventilation, oxygen consumption, cardiac output, and calculated work of the right ventricle all increased significantly.

The data suggest that patients with pulmonary emphysema tolerate poorly a hot environment, even though the humidity is low, and emphasize the need for air-conditioned surroundings in the management of these subjects during excessively warm weather.

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Biventricular origin of the pulmonary trunk with subaortic stenosis above the ventricular septal defect

*Henry N. Neufeld, M.D.**
*Patrick A. Ongley, M.D.***
*H. J. C. Swan, M.B., M.R.C.P., Ph.D.****
*E. Omer Burgert, Jr., M.D.***
*Jesse E. Edwards, M.D.*****
Rochester, Minn.

Edwards[1] and Becu and associates[2] have described a developmental complex with biventricular origin of the pulmonary trunk and subaortic stenosis. The ventricular septal defect is located anteriorly in the outflow tract of the right ventricle, without involvement of the membranous portion of the ventricular septum. The pulmonary artery is not transposed but overrides the ventricular septal defect. This malformation is also characterized by subaortic stenosis formed by a muscular ridge which lies across the outflow tract of the left ventricle and above the ventricular septal defect.[3] Associated obstructive anomalies of the aortic arch are constant. In all cases previously described the patients died in early infancy from pulmonary hemorrhage and edema, although one of us (J.E.E.) has observed a similar malformation in a 35-year-old man.

The purpose of this paper is to describe the pathologic-anatomic findings in three additional cases of this syndrome and to discuss the hemodynamics and clinical findings. Of further interest is the fact that in two of the three cases to be reported the patients were siblings (Cases 2 and 3), and identical pathologic malformations were found.

Report of cases

Case 1. An 8-year-old girl, born of a normal pregnancy and an uneventful delivery, appeared to be normal at birth. At 6 weeks of age a diagnosis of congenital heart disease was made when the baby was found to manifest cardiac failure, and she was digitalized. During the first 18 months of life the child was seriously ill, and gained weight poorly. By the age of 2 years her general condition seemed to improve. At 3 years of age a large benign ovarian tumor was removed. In the following years remarkable improvement in her general condition was noted, but respiratory infections occurred frequently during the last few years of her life.

The patient was seen first at the Mayo Clinic in March, 1959, when she was 8 years of age. Examination at that time revealed a somewhat undernourished girl who appeared to be chronically ill. Other pertinent factors were as follows: an absence of cyanosis and clubbing, normal femoral and radial pulses, no signs of congestive heart failure, overactivity of the heart with enlargement to the left, palpable second sound at the second left intercostal

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.
This study was supported in part by Research Grant No. H-4014, National Heart Institute, United States Public Health Service.
Received for publication Sept. 16, 1960.
*Special Appointee, Section of Pathologic Anatomy, Mayo Clinic. Cardiologist, Tel-Hashomer Government Hospital, Israel, on leave of absence.
**Section of Pediatrics, Mayo Clinic.
***Section of Physiology, Mayo Clinic.
****Section of Pathologic Anatomy, Mayo Clinic.

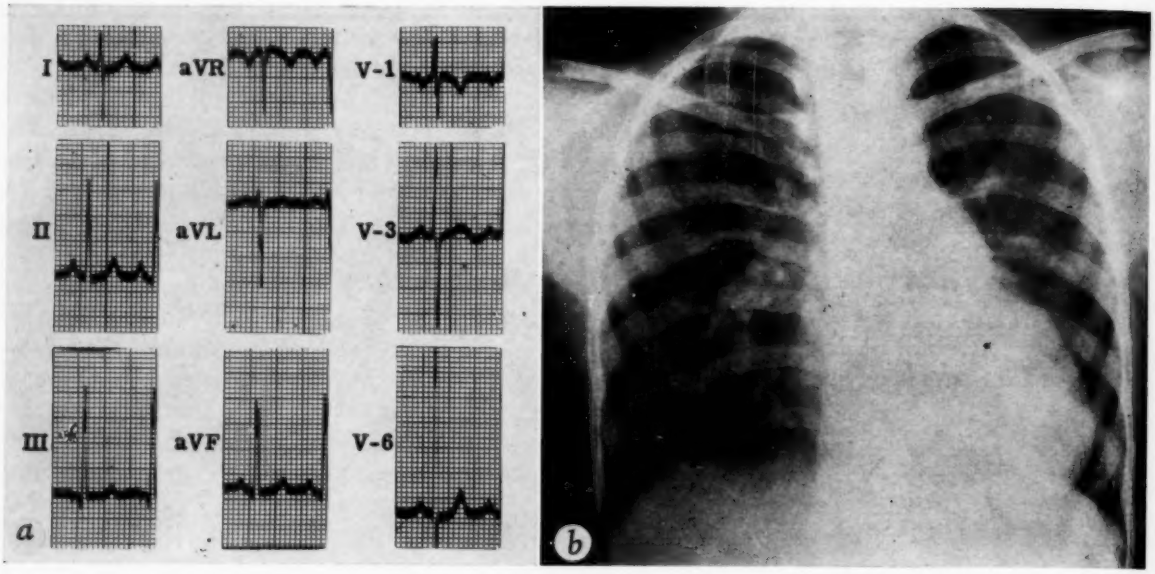


Fig. *1.* Case 1. *a*, The effects of left and right ventricular overload are shown by the electrocardiogram. *b*, Postero-anterior view of thorax, showing cardiac enlargement and prominence of the main pulmonary artery segment.

space, no thrill, normal first sound at the apex, and a narrowly split, greatly accentuated second sound at the second left intercostal space. A holosystolic murmur, Grade 3, was heard at the lower left sternal border. A different, higher pitched systolic murmur, Grade 2, was heard at the apex and was transmitted to the axilla and base of the left lung. In addition, an apical mid-diastolic rumble was noted and there was a short, high-pitched, low-intensity insufficiency type of blowing diastolic murmur at the pulmonary area.

An electrocardiogram (Fig. 1,*a*) showed normal sinus rhythm with a rate of 95, and the mean manifest electrical axis of the QRS was +85 degrees. The P-R interval was 0.12 second. The chest leads showed an RS pattern with a negative T wave in Lead V_1, and a qRs pattern with a positive T wave in Lead V_6. The electrocardiogram was interpreted as showing left ventricular overload and probable right ventricular overload.

The roentgenographic examination showed moderate cardiac enlargement and increased pulmonary vasculature. The pulmonary artery segment was prominent (Fig. 1,*b*).

In December, 1959, the right side of the heart was catheterized. A synopsis of the data is presented in Table I.

Of particular interest was an interatrial communication demonstrated by the passage of the catheter from the right atrium to the left atrium. The catheter then passed from the latter chamber into the left ventricle. The difference in oxygen saturation between samples of blood obtained from the pulmonary vein and from the left atrium suggested that a small right-to-left shunt occurred at the atrial level. A difference in pressure contour between the left atrium and the right atrium suggested that the communication was small, either a valve-component, patent foramen ovale or an exceedingly small atrial septal defect.

Also of interest were the measurements of pressures within the ventricles and the pulmonary artery compared to the pressure in the systemic artery. Ten recordings of simultaneous pressures in the systemic arteries, ventricles, and pulmonary artery were taken. All recordings showed that pressures in the ventricles and pulmonary artery were significantly in excess of pressures in the femoral and radial arteries.

At the ventricular level, both blood oxygen saturation and indicator-dilution curves indicated the presence of an interventricular communication with a dominant right-to-left shunt of approximately 45 per cent. The systemic blood flow was 5.6 liters per minute per square meter of body surface in contrast to a pulmonary blood flow of 3.1 liters. However, when the patient breathed 100 per cent oxygen, the pulmonary blood flow exceeded systemic blood flow

Table I. *Synopsis of data obtained during cardiac catheterization*

Site	*Pressure (mm. Hg)*	*Oxygen saturation (per cent of capacity)*
Superior vena cava	3*	69
Inferior vena cava	—	71
Right atrium	5/–2	69
Right ventricle	—	65
Pulmonary artery	118/71	66
Left ventricle	103/0–5	85
Radial artery	85/63	84
Femoral artery	88/70	83
Right pulmonary vein	5/0	95

*Mean pressure.

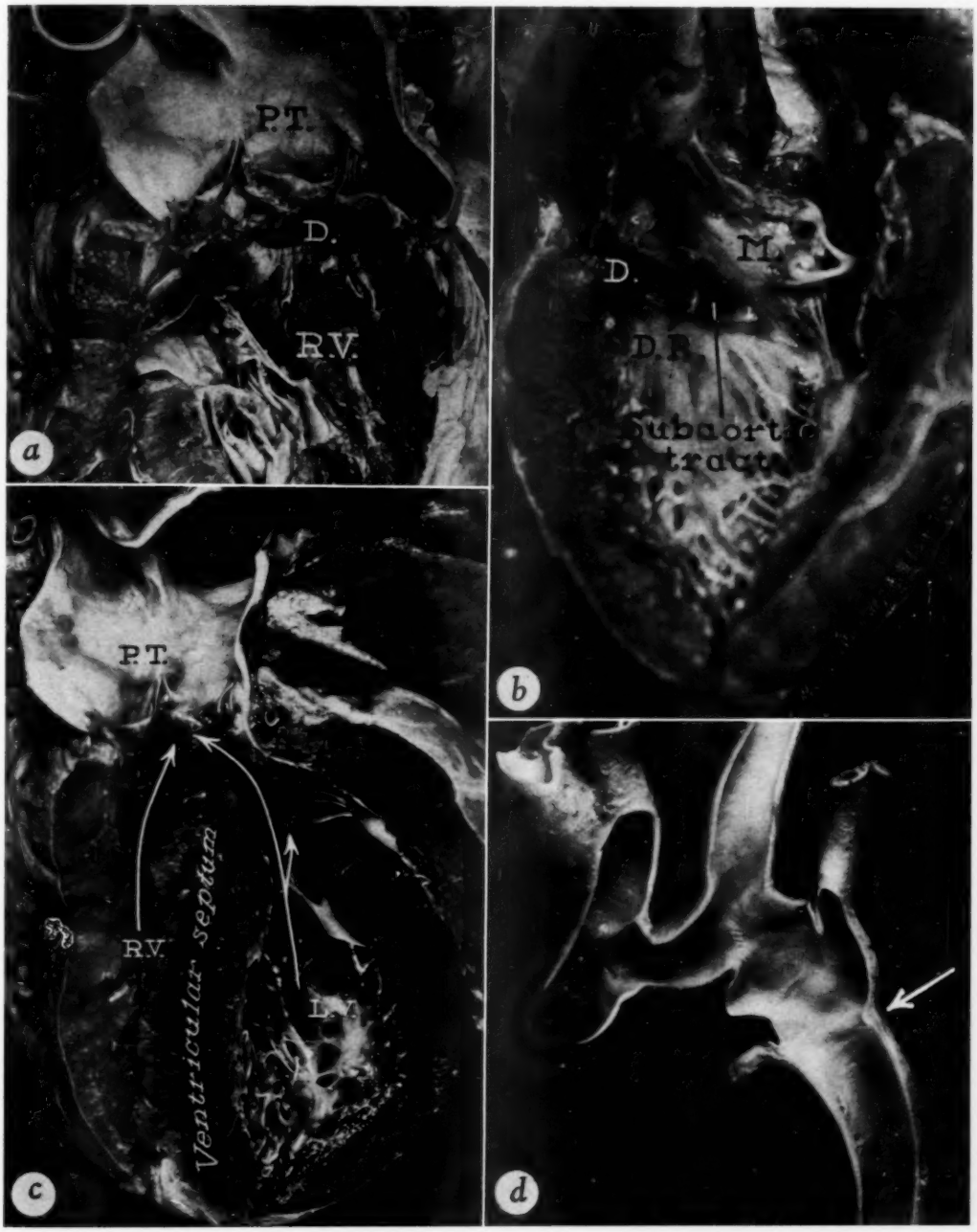


Fig. 2. Case 1. *a*, Right ventricle (*R.V.*) and pulmonary trunk (*P.T.*), showing the relationship of the ventricular septal defect (*D.*) to the pulmonary valve. The defect is immediately beneath the pulmonary valve. The biventricular origin of the pulmonary trunk is not so well appreciated in this perspective as in *c*. *b*, Left ventricular aspect. In the outflow tract of the left ventricle a ridge of muscle (*D.R.*) divides the outflow tract of the left ventricle into two portions. The anterior portion is that which communicates through the ventricular septal defect (*D.*) with the pulmonary trunk. The posterior subdivision of the outflow tract of the left ventricle is bounded anteriorly by the afore-mentioned dividing ridge and posteriorly by the anterior leaflet of the mitral valve (*M.*). The presence of the dividing ridge creates a stenotic subaortic tract. *c*, Sagittal section through the anterior walls of the two ventricles and through the ventricular septal defect to show the relationship of the two ventricles, the ventricular septal defect, and the pulmonary trunk. It is apparent that the pulmonary trunk lies in a position of biventricular origin and has communication with both ventricles. The left ventricular output is diverted partly through the ventricular septal defect to the pulmonary trunk and partly through the stenotic subaortic tract to the aorta. *d*, The aortic arch. The anterior wall has been removed, and the viewer sees the specimen from the front toward the back. The branches are normal. Beyond the origin of the left subclavian artery, and opposite the site of the ligamentum arteriosum, the superior and posterior walls show a small curtainlike infolding (*arrow*) which narrows the lumen slightly and represents a slight degree of the classic change in coarctation of the aorta.

by approximately 1.2 liters per minute per square meter of body surface. Under this circumstance, a left-to-right shunt of moderate magnitude was demonstrated, but a right-to-left shunt still accounted for approximately 20 per cent of the systemic blood flow.

Because of the electrocardiographic evidence of left ventricular overload, the roentgenographic evidence of increased pulmonary vasculature, and the dominant left-to-right shunt when the patient breathed 100 per cent oxygen, it was decided to attempt surgical closure of the ventricular septal defect, with a full appreciation of the high risk involved.

Surgical closure of the ventricular defect was carried out on March 3, 1960. No fall occurred in right ventricular pressure, and the patient died shortly after the operation was completed.

The essential findings at necropsy were limited to the cardiovascular system (Fig. 2). The heart showed the features of the developmental complex previously described. The pulmonary trunk, lying above and anteriorly to the ventricular septal defect, communicated with both ventricles (Fig. 2,*a*). Subaortic stenosis above the level of the ventricular septal defect was caused by a muscular ridge crossing the outflow tract of the left ventricle (Fig. 2,*b* and *c*). The aorta was continuous, and the branches arose in normal fashion. A classic deformity of aortic coarctation was found just distal to the origin of the left subclavian artery (Fig. 2,*a*). The degree of obstruction was minimal and evidently was not sufficient to cause a significant difference in pressure between radial and femoral arteries. Histologic examination of the lungs showed hypertensive vascular changes, Grade 4, as described by Heath and Edwards.[4] A representative section is shown in Fig. 3. Characteristic findings were formations of plexiform lesions with dilatation of vessels, thickening of the media, and intimal fibrosis.

Case 2. A newborn male infant died at the age of 3 days in 1958. The mother's pregnancy and delivery had been uncomplicated. On the second day after the infant's birth, increasingly progressive cyanosis was noted (specific location not described).

Neither the femoral nor the radial pulse was palpable. The heart was quiet, with a rate of 120. The first sound was normal; the second sound was single and accentuated. No murmurs were audible.

The roentgenogram showed moderate enlargement of the heart, with increased pulmonary vasculature (Fig. 4,*a*). In spite of supportive treatment, the child died suddenly on the third day of life.

The electrocardiogram showed a normal sinus rhythm with a mean electrical axis of the QRS complex of +140 degrees. The tracing showed a normal degree of right ventricular hypertrophy for the patient's age (Fig. 4,*b*).

Case 3. The sister of the infant in Case 2 was born 2 years later, in 1960. Again, the mother's pregnancy and delivery had been uneventful. After delivery, hoarseness and differential cyanosis were noted in the child. Cyanosis was present and equal in the arms and feet, but was not present in the cheeks. The child was placed in an oxygen tent, but the cyanosis persisted.

Blood pressures taken by the flush method were equal in the arms and legs. The cardiac rate was 140 beats per minute, and the heart was overactive. The first cardiac sound was normal, and the second sound was narrowly split and accentuated.

A Grade 3 systolic murmur and a Grade 2 diastolic murmur were heard over the left side of the sternum.

Roentgenographic examination showed evidence of an enlarged heart and prominent pulmonary vasculature (Fig. 5,*a*). The electrocardiogram showed normal sinus rhythm. The mean value for the manifest electrical axis was approximately +120 degrees (Fig. 5,*b*).

In spite of supportive treatment, the child did not improve; she died on the third day of life.

Pathologic examination of the heart and great vessels in this patient and the brother (Case 2) showed identical findings (Fig. 6). Therefore, they are described together.

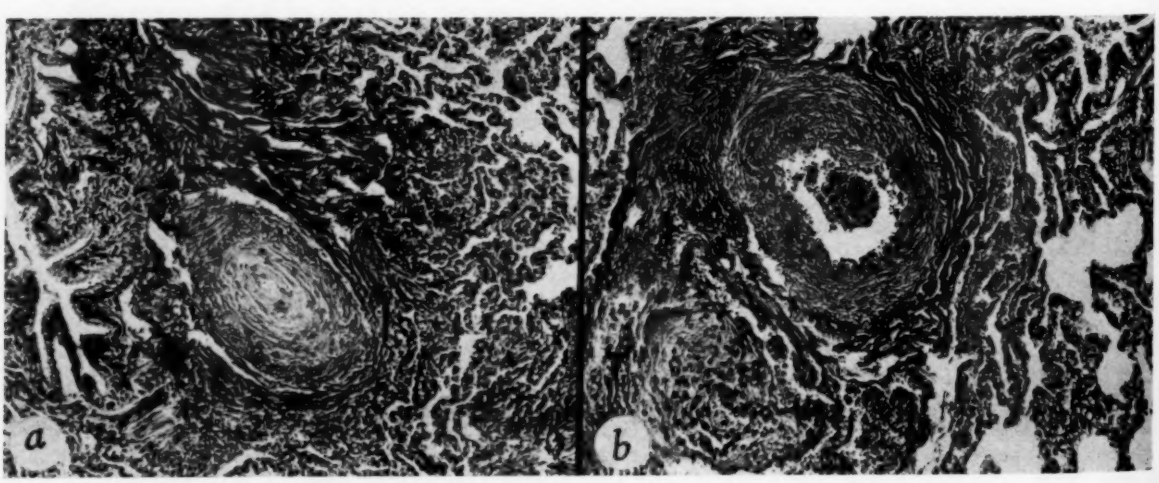
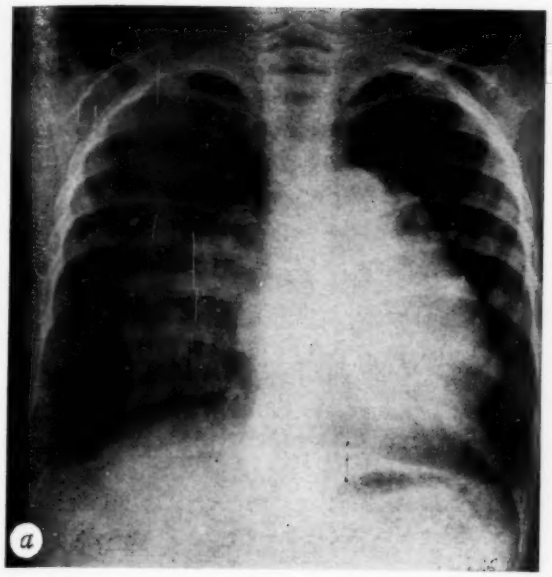


Fig. 3. Case 1. A large muscular artery shows medial hypertrophy. *a*, With pronounced nonspecific intimal fibrous thickening (hematoxylin and eosin; ×75). *b*, With plexiform lesion (in lower left-hand corner) (hematoxylin and eosin; ×100).



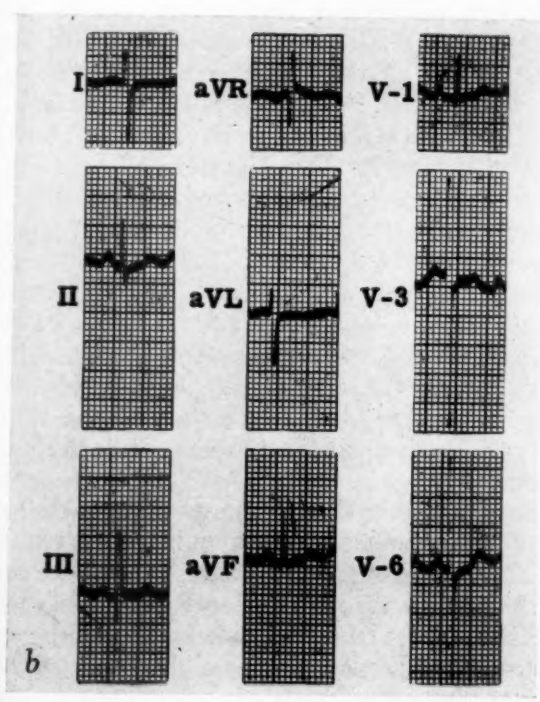
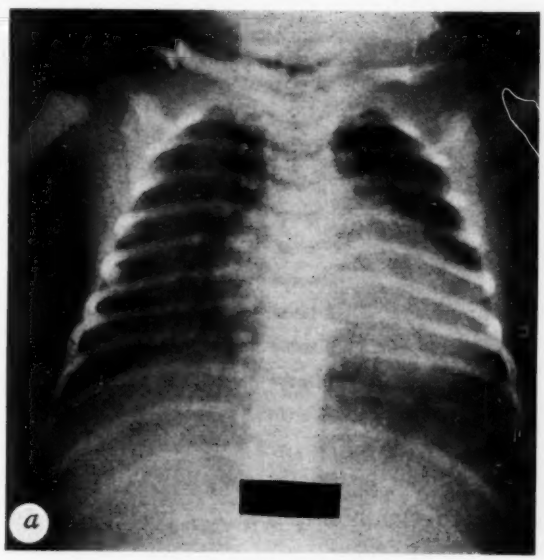


Fig. 4. Case 2. *a*, Posteroanterior view of thorax, showing cardiomegaly with increased pulmonary vasculature. *b*, Normal sinus rhythm with a mean electrical axis of the QRS complex of +140 degrees.



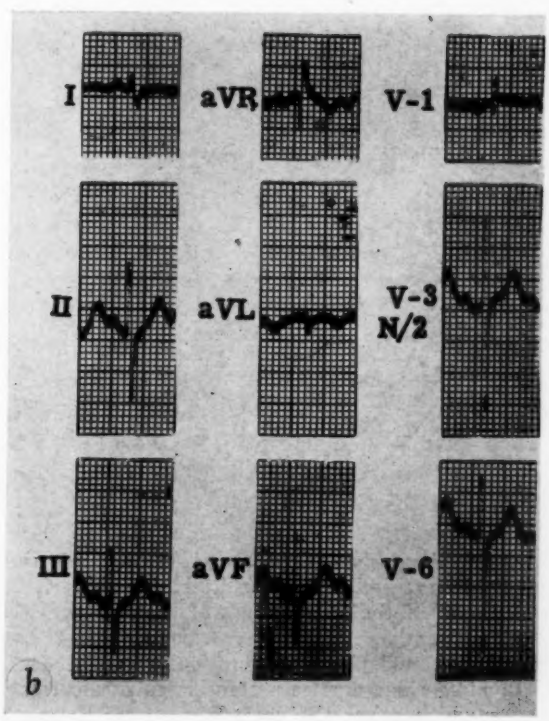


Fig. 5. Case 3. *a*, Posteroanterior view of thorax, showing cardiomegaly with increased pulmonary vasculature. *b*, Normal sinus rhythm, with a mean electrical axis of +120 degrees.

PATHOLOGIC FINDINGS IN CASES 2 AND 3. In each case the heart showed a ventricular septal defect in the basal portion of the ventricular septum at an anterior position above the crista supraventricularis. The defect was close to the origin of the pulmonary trunk, and the latter exhibited biventricular origin, in view of its close association with the ventricular septal defect (Fig. 7,*a* and *b*).

A muscular crest divided the outflow tract of the left ventricle into two portions, one leading to the ventricular septal defect and the other representing a stenotic subaortic tract, above which arose the aorta (Fig. 6). The ascending aorta ended by dividing into the two common carotid arteries.

The pulmonary trunk was wide and gave rise to the two pulmonary arteries, after which the ductus

arteriosus led into the descending aorta (Fig. 8,*a* and *b*). The left and right subclavian arteries arose from their respective sides of the descending aorta below the level of the ductus arteriosus. The right subclavian artery passed behind the esophagus to reach a normal position in the right axilla. There was no ductus arteriosus on the right side (Figs. 8,*c* and 9). Histologic examination of the lungs in Cases 2 and 3 showed vascular changes, Grade 1, as described by Heath and Edwards. The media of the muscular pulmonary arteries was thickened; intimal fibrosis was not present, but the adventitia was thick and fibrous. The type of change was that associated with pure left-to-right shunts among patients who have ventricular septal defect (Fig. 10).

Comment

Pathologic-anatomic features. In this complex the ventricular septal defect lies anterior to the membranous portion of the ventricular septum and above the papillary muscle of the conus. From the right ventricular view the defect opens into the distal portion of the right ventricular outflow tract. A portion of the upper edge of the defect is formed by the pulmonary valvular tissue at the commissure between the left and right pulmonary cusps.

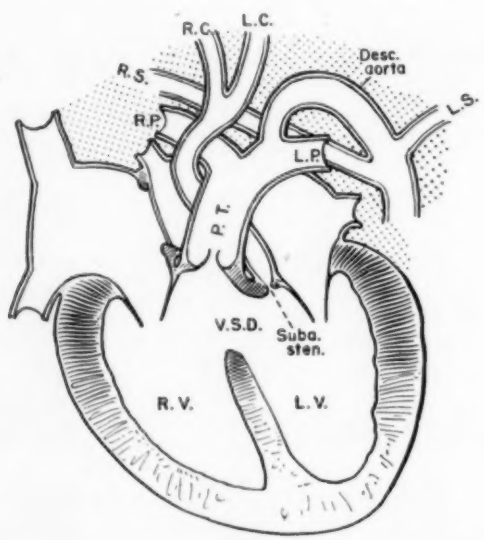


Fig. 6. Diagrammatic portrayal of the essential anatomic features within the heart in Cases 1, 2, and 3, and of the arrangement of the great vessels in Cases 2 and 3. There is biventricular origin of the pulmonary trunk above the ventricular septal defect. A dividing ridge creates a stenotic subaortic tract, above which arises the ascending aorta. In these particular instances (Cases 2 and 3), there was interruption of the aortic arch, wherein the ascending aorta terminated by dividing into the right and left common carotid arteries (*R.C.* and *L.C.*). The descending aorta communicates with the pulmonary arterial system by way of a patent ductus arteriosus. The two subclavian arteries arise opposite each other from the upper portion of the descending aorta. The right subclavian artery (*R.S.*) passed behind the esophagus to reach the right side of the body. In this particular instance, supply of the descending portion of the body and of the subclavian arteries by the right ventricle was the basis for cyanosis of the arms and lower portion of the body, whereas the head failed to show this abnormal sign.

The outflow tract of the left ventricle is divided by a muscular ridge which runs from the base of the anterior leaflet of the mitral valve to the anterior wall of the left ventricle. This muscular ridge divides the outflow tract of the left ventricle into two parts: a narrow subaortic tract beyond which the aorta arises, and a part which is connected with the ventricular septal defect.

Additional obstructive malformations of the aorta were noted in all cases in which the intracardiac malformations described in this paper and in previous reports are present. Some cases are associated with interruption of the aortic arch; others show coarctation or hypoplasia of the aortic arch. Anomalous origin of the right and left subclavian arteries from the descending aorta represents the early embryonic onset of this defect. Another interesting feature in the cases presented herein is the occurrence of the same malformation in siblings.

Hemodynamics. Becu and associates[2] emphasized that in this anomaly a left-to-right shunt at the ventricular level probably exists during fetal life because of the subaortic stenosis above the ventricular septal defect. Such a shunt would reduce aortic flow and increase pulmonary flow. Under these circumstances the pulmonary trunk dilates and overrides progressively. The reduced flow through the aorta, on the other hand, might be responsible for the tendency toward hypoplasia, or possibly even toward interruption of the aortic arch. Data do not establish these points, and the aortic malformation may be derived from the same stimuli which cause the intracardiac malformation.

Case 1 in this series is, to the best of our knowledge, the first case reported in the literature in which catheterization data were interpreted. The physiologic study showed the interesting features discussed below.

The finding of a consistently higher pressure in the right and left ventricles and pul-

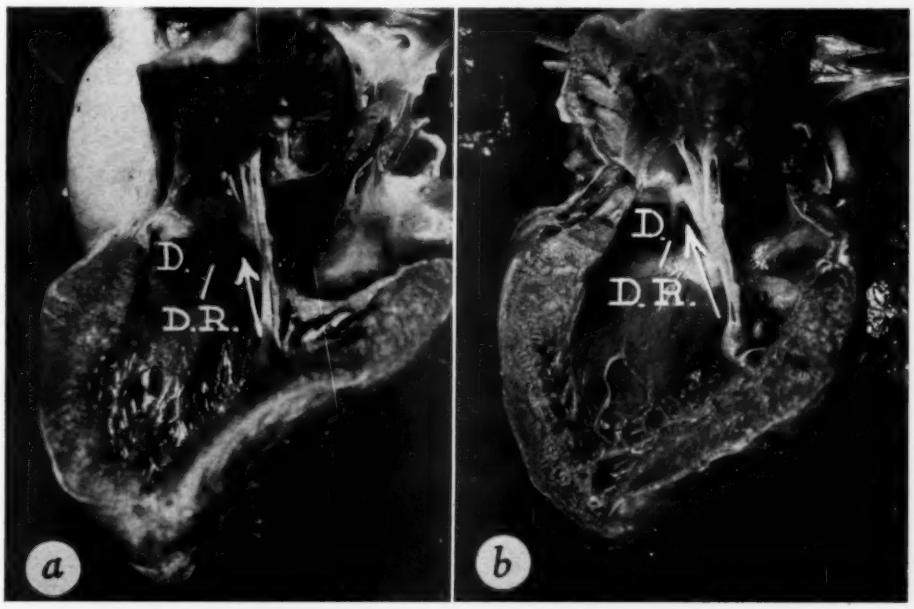


Fig. 7. The left ventricular outflow tracts in the siblings (Cases 2 and 3) show the virtually identical structural abnormalities of the two cases. *a*, Case 2; *b*, Case 3. The perspective is essentially that shown in Fig. 2,*b* (Case 1). The dividing ridge (*D.R.*) separates the outflow tract of the left ventricle into two channels, one leading to the ventricular septal defect (*D.*) and the other posteriorly to the stenotic subaortic tract (*arrow*).

monary artery than in the systemic arteries is of great significance in establishing the diagnosis of the intracardiac malformation in this instance. In a comparison of simultaneously recorded aortic and radial arterial pressures, Kroeker and Wood[5] have shown that amplification of the systolic peak at the peripheral artery occurs in an average of 11 per cent. Thus, for example, a pressure pulse recorded simultaneously at the aortic root and radial artery could be expected to show pressure values of 100 and 110 mm. Hg systolic, respectively. The converse is rarely if ever seen. Occasionally, in patients with rheumatic heart disease in whom the cardiac output is reduced, or in patients with severe aortic stenosis and reduced cardiac output, pressures in the systemic and central arterial circulations may be equal. In Case 1, however, we found a significant difference. Although the ventricular pressures were equal and were transmitted without diminution into the pulmonary artery, these pressures significantly exceeded the systemic arterial pressure. If any systolic amplification occurred in this case, the true pressure gradient between the ventricles and the aortic root would have been somewhat greater than the given values suggested initially.

All other conditions being unaltered, the combination of subaortic or aortic valvular stenosis above a ventricular septal defect should lead to a marked increase in pulmonary blood flow. However, as with other cases of ventricular septal defect, there is no reason why progressive and severe pulmonary vascular disease should not develop in such patients, so that the increased resistance offered to ejection of blood from the ventricles through the aortic valve might become balanced by increased pulmonary resistance and might even be exceeded by the resistance offered by the diseased pulmonary vascular bed. As a result, even though the pressure relationships would remain the same, the magnitude of the left-to-right shunt would fall. If the pulmonary vascular resistance became higher than the resistance to flow through the aortic valve, a right-to-left shunt might appear. Such phenomena appear to have developed in Case 1.

The histologic changes in the pulmonary vessels found in Case 1 showed Grade 4 changes (Fig. 3)[4] and were compatible with

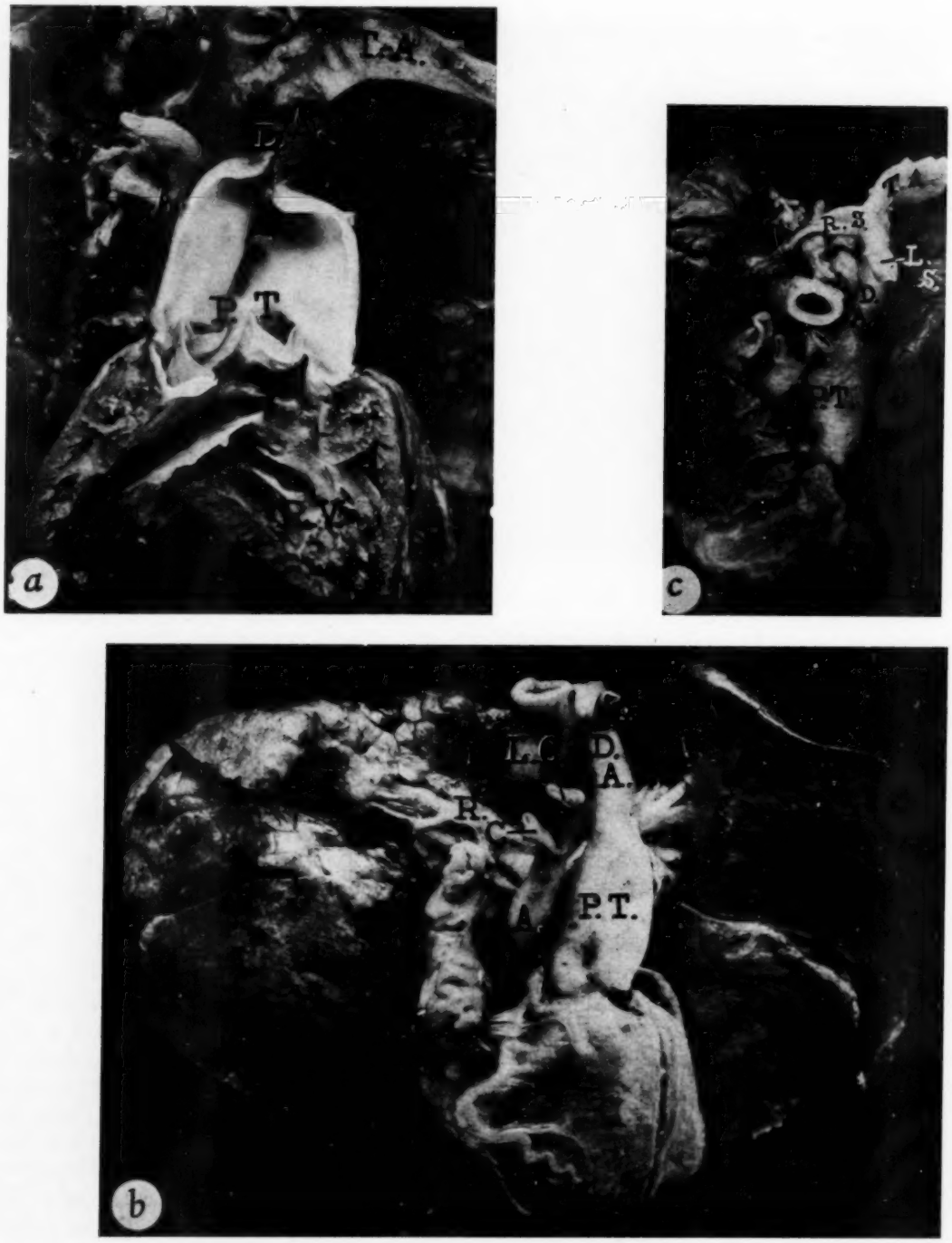


Fig. 8. Case 2. The features shown are essentially like those observed in Case 3. *a*, Right ventricle and great vessels. The ventricular septal defect, which lies immediately beneath the origin of the pulmonary trunk (*P.T.*), is seen from the right ventricular aspect (*R.V.*). In this instance, as in all others of this developmental syndrome, the pulmonary trunk showed biventricular origin. The ascending aorta (*A.*) is divided into its two terminal branches, the two carotid arteries. The thoracic portion of the descending aorta (*T.A.*) has no connection with the ascending aorta and takes origin from the pulmonary arterial system by way of the ductus arteriosus (*D.A.*). *b*, Anterior view of heart and great vessels, showing the termination of the ascending aorta (*A.*) into the right common carotid (*R.C.*) and the left common carotid (*L.C.*) arteries. The pulmonary trunk is wide and the ductus arteriosus (*D.A.*) represents the channel of continuity between the pulmonary arterial system, on the one hand, and the descending aorta, on the other. *c*, The great vessels viewed from above, showing the continuity of the descending thoracic aorta (*T.A.*) with the pulmonary arterial system (*P.T.*) by way of the patent ductus arteriosus (*D.A.*). The left subclavian artery (*L.S.*) and the right subclavian artery (*R.S.*) both arise from the descending thoracic aorta beyond the ductus arteriosus. In this perspective the position of the right subclavian artery behind the trachea and esophagus is shown.

severe elevation of pulmonary vascular resistance.

In the two cases with interruption of the aortic arch (Cases 2 and 3) the hemodynamics must have differed from those in Case 1. In Cases 2 and 3 it is assumed that only left-to-right shunts existed within the heart. In these two patients, both ventricles and the pulmonary artery were in the same systolic compartment. The ascending aorta was separated from this compartment proximally by the subaortic obstruction, and distally by the interruption of the aortic arch. Since the ascending and the descending aorta are separated, the blood supply to the descending aorta comes from the pulmonary artery via the ductus.

We can assume that the systolic pressure was equal in both ventricles, in the pulmonary artery, and in the descending aorta, whereas the pressure in the ascending aorta must have been lower than in these vascular segments or ventricles.

If both subclavian arteries arise below the interruption of the arch, as in Cases 2 and 3, the pressures in the brachial and femoral arterial systems would be equal and higher than those in the arteries supplying the neck and head. The arms and legs receive blood from the pulmonary artery through the ductus, and the head receives its supply from the ascending aorta.

In patients with anatomic arrangements like those in Cases 2 and 3, cyanosis may be seen only in those parts of the body supplied by the aorta beyond the interruption. Depending on the degree of left-to-right or right-to-left shunt at the ventricular level, cyanosis seen in the portion of the body supplied by the proximal aorta may be of a different degree (less blue) than that (bluer) seen in the portion of the body supplied by the descending aorta.

The recognition of this entity and its differentiation from the more commonly encountered ventricular defect with pulmonary hypertension is of some practical importance. In the assessment of the operability of patients with ventricular septal defect and pulmonary hypertension the electrocardiographic finding of left ventricular overload has been of great assistance as an indication of the presence of a dominant left-to-right shunt. It is imperative to exclude other causes of left ventricular overload, particularly those associated with aortic stenosis or mitral insufficiency. In Case 1 these lesions were considered, but the typical murmur of aortic stenosis could not be distinguished from the prominent murmur of ventricular septal defect. In retrospect, the consistent elevation of ventricular and pulmonary arterial pressures above systemic pressure should have led to a more careful consideration of the presence of aortic or subaortic stenosis.

Summary

Three cases are reported that presented a complex of congenital cardiac anomalies which consisted of biventricular origin of the pulmonary trunk with subaortic stenosis above a ventricular septal defect. In Case 1 the hemodynamic findings obtained at cardiac catheterization showed consistently higher ventricular and pulmonary arterial pressures when these were compared to systemic arterial pressure. Two patients were siblings with identical anatomic findings (Cases 2 and 3). Both of these patients had associated interruption of the aortic arch. The descending aorta, which

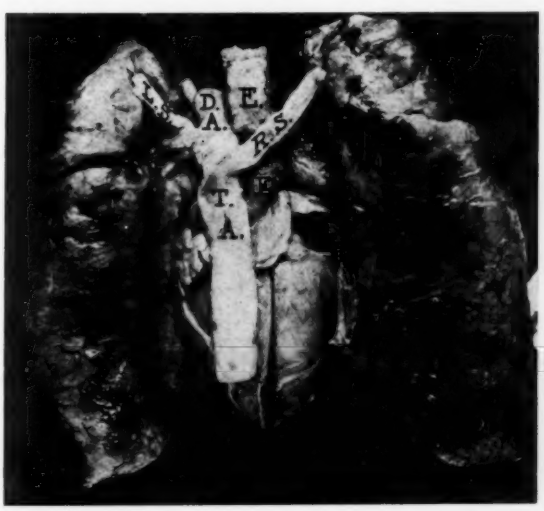


Fig. 9. Posteroanterior view of the heart and lungs (Case 3), showing arrangements which were duplicated in Case 2. The descending thoracic aorta (*T.A.*) takes origin from the ductus arteriosus (*D.A.*), which represents the channel of communication between the descending thoracic aorta and the pulmonary arterial system. The two subclavian arteries are seen to arise from the upper portion of the descending aorta just beyond its origin in the ductus arteriosus. *L.S.*: Left subclavian artery. The right subclavian artery (*R.S.*) passes behind the esophagus (*E.*) to reach the right side of the body.

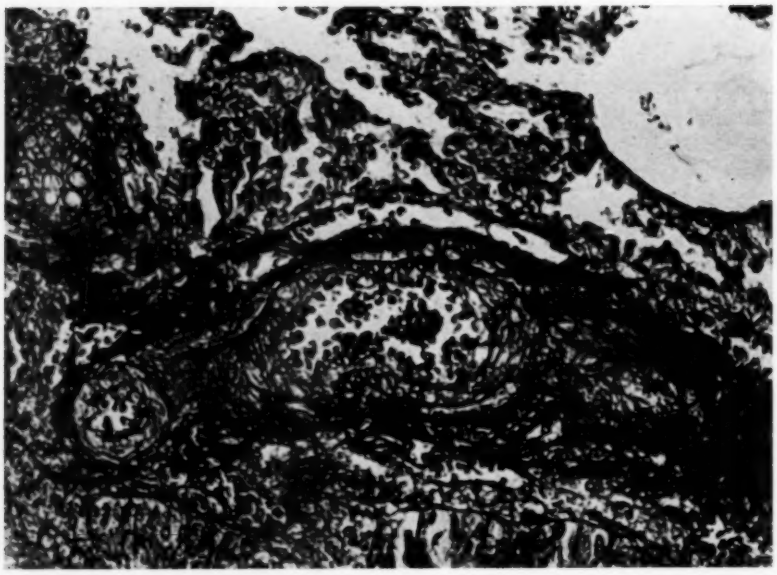


Fig. *10.* Case 3. A muscular artery has been cut in both cross and longitudinal sections. The vessel shows medial hypertrophy and prominent endothelial cells but no intimal fibrosis (elastic tissue stain; ×200).

gave rise to the subclavian arteries, communicated with the right ventricle through a patent ductus arteriosus. In one of the patients (Case 3), differential cyanosis was noted: the upper and lower extremities were cyanotic but the head was not cyanotic. Mild coarctation of the aorta was present in the third patient (Case 1).

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The auscultatory findings in primary myocardial disease

W. Proctor Harvey, M.D.
Joseph K. Perloff, M.D.
Washington, D. C.

Auscultation of the heart has been of great value in the clinical diagnosis and evaluation of patients with primary myocardial disease.[1] The myocardial abnormalities in this category occur in the absence of acquired valvular heart disease, coronary artery disease, hypertension, or congenital malformations.[2-5] The group includes: (1) myocarditis[6-10] (associated with infectious diseases, collagen diseases, sarcoidosis, physical agents, toxic agents, and of unknown cause); (2) myocardial hypertrophy of unknown etiology[11]; (3) infiltrative diseases of the myocardium[12-15] (neoplasms, amyloidosis, etc.); (4) nutritional cardiopathy[16-18]; (5) endocardial fibroelastosis[19]; (6) endomyocardial fibrosis[20,21]; (7) familial cardiomegaly[22]; (8) metabolic heart disease[23-26] (thyrotoxicosis, hemochromatosis, glycogen storage disease, gargoylism, etc.); (9) cardiomyopathies associated with neuromuscular disorders[27,28] (progressive muscular dystrophy, dystrophia myotonica, Friedreich's ataxia). The auscultatory features are outlined in Table I; they are the results of conduction defects, ectopic rhythms, myocardial failure, or associated pericardial involvement. A combination of these findings is frequently present.

Diastolic gallop rhythm, ventricular and/or atrial, is common (Figs. 1-5, 7). At times the two gallop sounds may coincide, resulting in a summation gallop rhythm. In the presence of congestive heart failure a ventricular gallop has been a constant finding. An atrial gallop is frequently observed and may be more evident with delayed atrioventricular conduction. However, the atrial gallop may occur even when the P-R interval is normal. The diagnosis of primary myocardial disease should be considered when a patient with heart disease presents with a ventricular and/or atrial diastolic gallop, cardiomegaly, and other symptoms or signs of cardiac decompensation unexplained by the usual causes of heart disease.[4] The pulmonary second sound is generally increased in the presence of cardiac decompensation (Fig. 1, right lower strip). Occasionlly, the combination of both ventricular and atrial diastolic gallop sounds produces a diastolic rumble which simulates mitral stenosis. In fact, the patient whose tracings are shown in Fig. 2 was thought to have rheumatic mitral stenosis and was referred to our hospital to be evaluated for commissurotomy. After a complete study, including cardiac catheterization, the diagnosis of idiopathic myocarditis was made. She has been followed in the Cardiac Clinic for

From the Department of Medicine, Georgetown University School of Medicine, Division of Cardiology, Georgetown University Hospital, Washington, D.C.
Supported in part by Grants H-3319 and H-5551, SRC from the U.S. Public Health Service, National Institutes of Health, Bethesda, Md., Washington Heart Association, Metropolitan Heart Guild, and Special Cardiac Research Fund.
Received for publication Sept. 23, 1960.

the past 6 years and has shown definite improvement on steroid therapy, which resulted in a diminution of heart size, disappearance of the gallop rhythm, and marked symptomatic improvement. When the steroids were discontinued, her symptoms and signs of heart failure, including gallop rhythm, and the diastolic rumble reappeared. In addition, complete heart block developed. These features again regressed with reinstitution of corticoid therapy.

The ventricular diastolic gallop has been a constant finding in patients with cardiac decompensation, and often has been one of the first clues indicating the presence of heart failure. The patient may subsequently improve with the institution of digitalis, restriction of sodium, and diuretics. At other times, only an atrial gallop is noted, as illustrated in Fig. 3 (left lower tracing), in a 25-year-old man with cardiac enlargement and right bundle branch block. Cardiac catheterization disclosed no unusual

Table I. *Auscultatory abnormalities in myocarditis*

Conduction Defects:

I. A-V node
  A. P-R interval prolongation
    1. Decreased intensity of S_1
    2. Atrial gallop rhythm
    3. Atrial sound with prolonged vibrations (atrial murmur)
  B. Second-degree heart block
    1. Isolated atrial sounds
  C. Complete heart block
    1. Variation in intensity of S_1
    2. Atrial sounds
II. Bundle branch block
  A. Right bundle branch block
    1. Delay in P_2 with wide splitting of S_2
  B. Left bundle branch block
    1. Delay in A_2 with paradoxical splitting of S_2

Ectopic Rhythms:

I. Extrasystoles
  A. Atrial premature contractions
  B. Ventricular premature contractions
II. Atrial fibrillation
III. Ventricular tachycardia
  A. Multiple sounds and variation in intensity of S_1
    1. Combination of atrial gallop, split S_1, split S_2, and ventricular diastolic gallop

Myocardial Failure:

I. Gallop rhythm
  A. Ventricular diastolic gallop
  B. Summation gallop—fusion of atrial and ventricular diastolic gallops
  C. Mid-diastolic murmur
    1. Ventricular diastolic gallop with prolonged vibrations
    2. Proximity of atrial and ventricular diastolic gallops
II. Pulmonary hypertension
  A. Narrow splitting of S_2 with loud P_2
III. Relative atrioventricular valvular insufficiency
  A. Mitral insufficiency
  B. Tricuspid insufficiency

Associated Pericarditis:

I. Pericardial friction rubs
  A. Two components
    1. Sinus rhythm—ventricular systolic and atrial components
    2. Atrial fibrillation—ventricular diastolic and ventricular systolic components
  B. Three components
    1. Sinus rhythm—atrial, ventricular systolic, and ventricular diastolic components

findings. No signs of heart failure were present during this period of observation, but several years later his physician reported that he had been admitted to another hospital because of pulmonary edema. Various examples of primary myocardial disease are shown in Figs. 1 through 8. Fig. 4 shows the tracings of two patients with lupus erythematosus, one case with sarcoidosis, and the other of unknown cause. The patient with myocardial disease of unknown cause (autopsy) whose tracings are shown in Fig. 1 was followed for several years, and both atrial and ventricular diastolic gallops were observed clinically. At times a diastolic rumble was heard, and at other times, particularly when the rate was rapid, a type of summation gallop rhythm appeared. A faint systolic murmur at the cardiac apex was generally present, and a greatly accentuated pulmonic second sound with close splitting of the second heart sound was heard in the pulmonary area and at the left sternal border.

A systolic murmur is a frequent finding in primary myocardial disease (Figs. 1 through 6) and represents either an innocent outflow, ejection murmur, or a pansystolic murmur of relative mitral and/or tricuspid valvular insufficiency. The murmur generally varies between Grade 2 and Grade 4 (on the basis of grading 1 through 6), and often leads to the erroneous diagnosis of rheumatic heart disease, such as mitral insufficiency, or a congenital malformation, such as ventricular septal defect. A patient recently observed had a Grade 3 to 4 pansystolic murmur, best heard at the lower left sternal border and transmitted to the left axilla, lung bases, and lower left

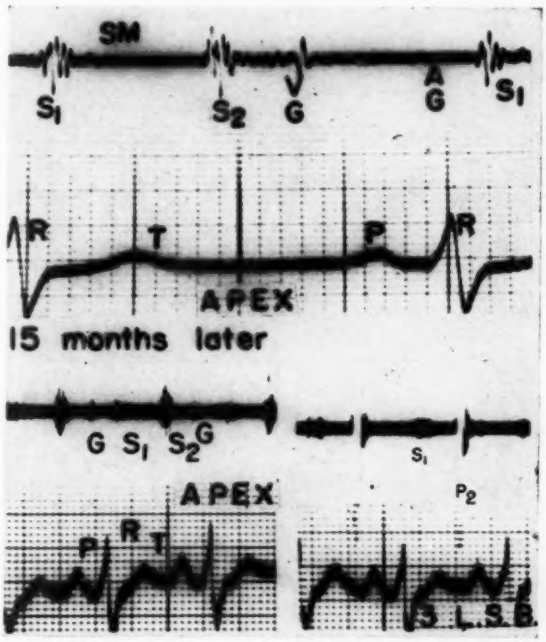

Fig. *1.* Thirty-seven-year-old man who had progressive refractory heart failure for approximately 1½ years before death. *Upper tracing:* Note atrial (*AG*) and ventricular (*VG*) diastolic gallops and systolic murmur (*SM*). Fifteen months later (*lower strips*) he had advanced heart failure, summation gallop (*G*), and loud second sound (P_2). Autopsy finding: chronic myocarditis, idiopathic.

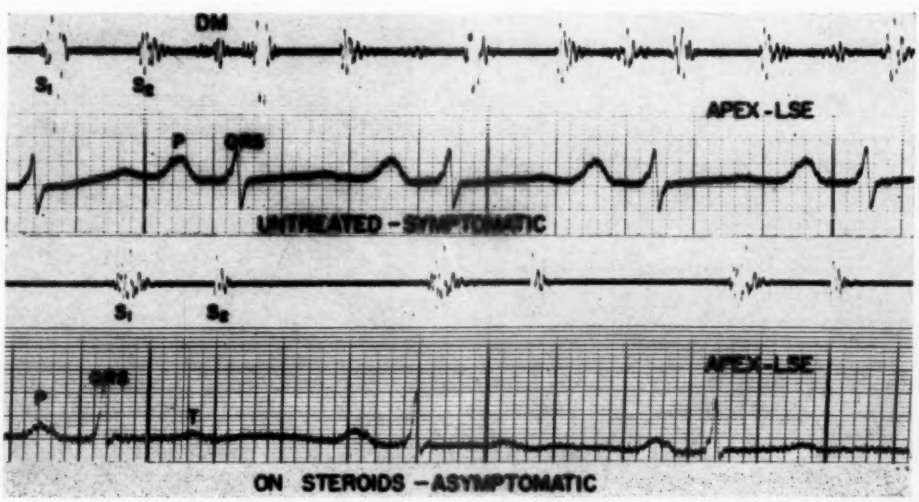

Fig. *2.* Thirty-five-year-old woman with chronic idiopathic myocarditis, controlled on steroid therapy. *Upper tracing:* Congestive failure. Note diastolic rumble (*DM*). *Lower tracing:* No failure. On steroids. No murmurs or gallops.

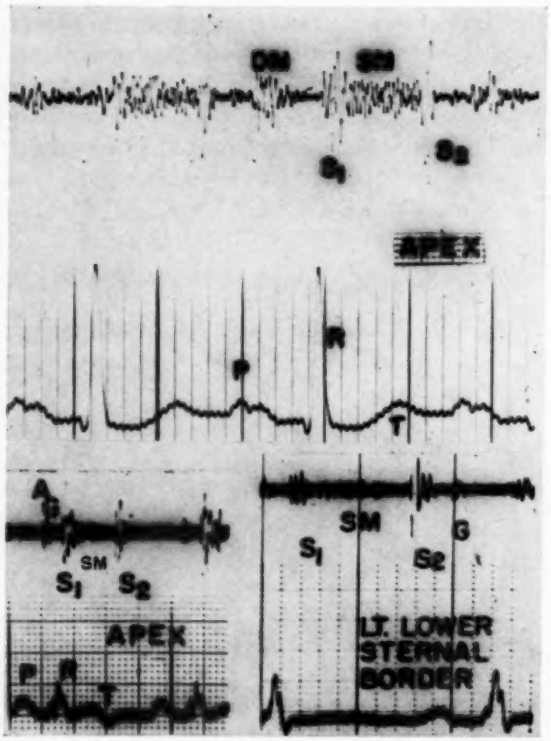

Fig. 3. Fibroelastosis—3 cases (2 suspected and 1 definite). *Upper tracing:* 2½-year-old girl with fibroelastosis (proved by biopsy) and coarctation. Note systolic murmur (*SM*) and diastolic rumble (*DM*). *Lower left tracing:* 25-year-old man with cardiac enlargement, atrial gallop (*AG*), and right bundle branch block, who had Grade 2 to 3 apical systolic murmur (*SM*). Normal cardiac catheterization. He had pulmonary edema several years later. *Lower right tracing:* Infant girl, 3 months of age, with congestive failure, râles, and hepatomegaly. Note systolic murmur (*SM*) and gallop (*G*).

interscapular region. There was no evidence of a shunt or of organic valvular disease at the time of catheterization of the right and left sides of the heart. A ventricular diastolic gallop was present at the apex. Primary myocardial disease, probably fibroelastosis, was suspected. Fig. 7 illustrates tracings from two patients with myocardial disease of unusual origin: one patient had Wegener's granulomatosis,[30] and the other had obscure eosinophilia and some clinical features suggestive of restrictive myocardial disease, such as seen in constrictive pericarditis.[31]

The presence of conduction defects, such as right or left bundle branch block, may produce abnormal splitting of the first and second heart sounds. In complete right bundle branch block, wide splitting of the second heart sound during expiration, with further increase in splitting during inspiration (Fig. 8), is characteristic[32] and is best heard at the pulmonary area and at the third intercostal space, left sternal border. In addition, the first heart sound is frequently widely split. With complete left bundle branch block,[32] the splitting of the second sound is paradoxical (reversed sequence of semilunar valvular closure), re-

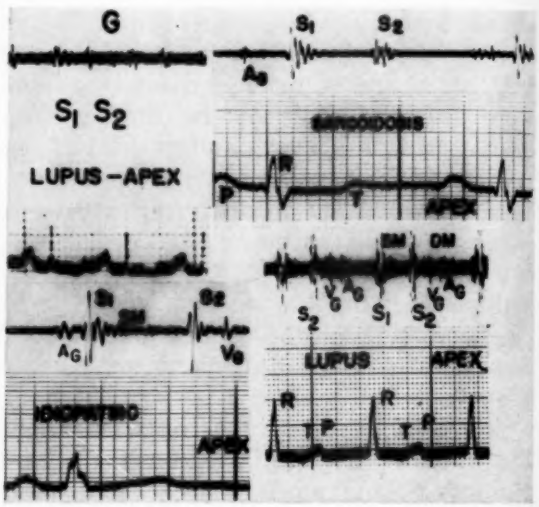

Fig. 4. Myocardial disease in 4 patients. Note frequency of gallop rhythm (*G*, A_G, V_G). Systolic murmur (*SM*) in lower two. Diastolic rumble (*DM*) heard in one (*lower right*).

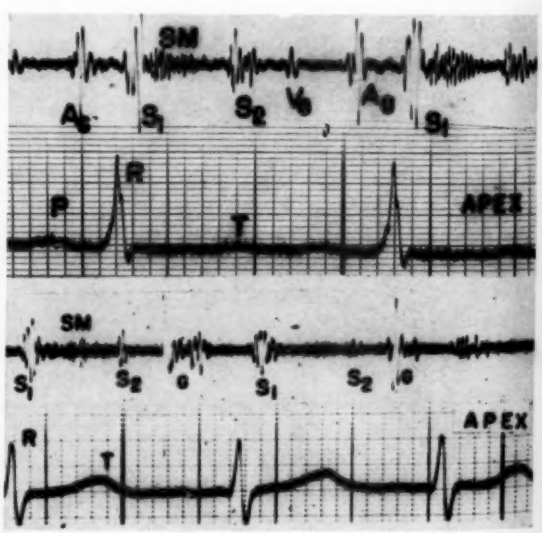

Fig. 5. Thyrotoxicosis in 2 patients. *Upper tracing:* 38-year-old woman. Note atrial (*AG*) and ventricular (*VG*) gallops and systolic murmur (*SM*). *Lower tracing:* 42-year-old man. Atrial fibrillation. Note systolic murmur (*SM*); ventricular gallop (*G*) had several components producing a rumble quality.

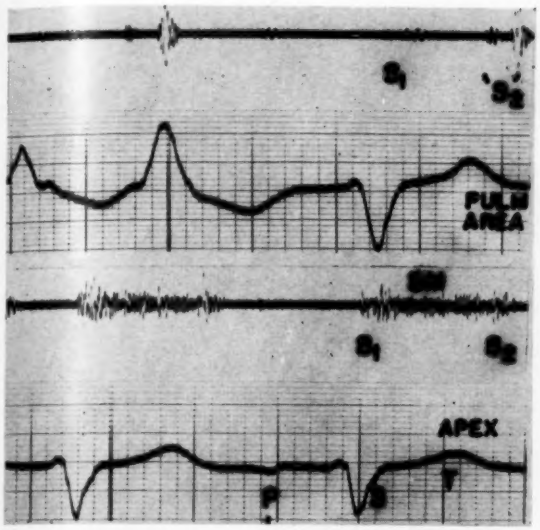

Fig. *6*. Chronic myocarditis, idiopathic, in a 55-year-old man who had conduction defect, short paroxysms of ventricular irregularity. Note pansystolic murmur (*SM*) at apex (*lower tracing*).

sulting in a widely split second sound during expiration and a single or closely split second sound during inspiration. This abnormal splitting of sounds may be heard in conjunction with gallop rhythm and other auscultatory findings already discussed.

The majority of our patients have had a regular sinus rhythm, but occasionally an arrhythmia is the earliest manifestation of primary myocardial disease.[2] Fig. 9 shows the electrocardiogram of a 17-year-old boy who had a grossly irregular ventricular rhythm due to the presence of multifocal ventricular premature contractions, and, at times, atrioventricular dissociation.* This patient's arrhythmia started when he had Asian influenza 2 years prior to admission. Three days after this electrocardiogram was taken, the patient died suddenly. Postmortem examination revealed chronic interstitial myocarditis with patchy areas of subendocardial fibrosis. In other patients, various arrhythmias, including atrial fibrillation or ventricular tachycardia, may contribute to the abnormal auscultatory findings. Fig. 10 represents a composite of the auscultatory manifestations of primary myocardial disease. These features may be observed individually or in various combinations, and together with the complete clinical evaluation of the patient, they often enable the physician to suspect the

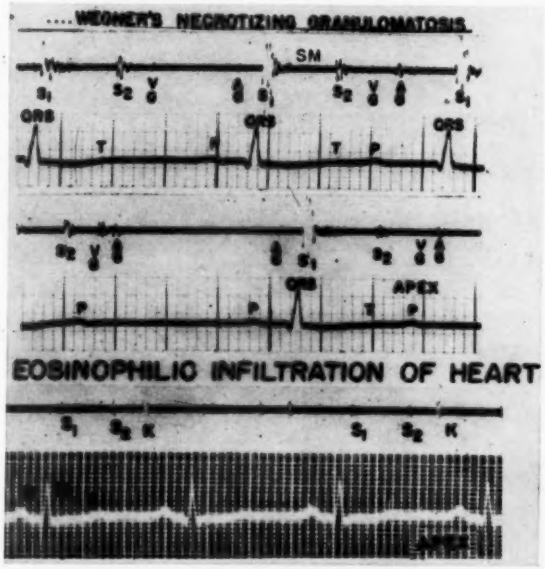

Fig. 7. Two patients with myocarditis of unusual origin. Upper two strips are continuous tracing of 44-year-old woman. Note faint systolic murmur (*SM*). Atrial (*AG*) and ventricular (*VG*) gallops vary with change in P-R relationship. When gallops are close, rumble quality is produced. *Lower strip:* 26-year-old man with heart failure of obscure origin. Had marked eosinophilia and findings consistent with restrictive myocardial lesion. Had loud diastolic knock sound (*K*). Systolic murmur was also heard.

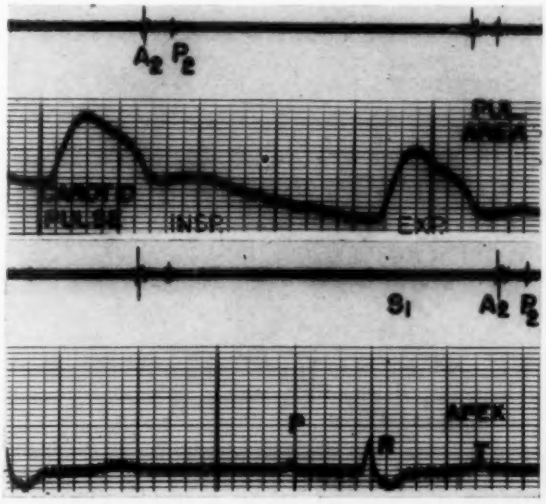

Fig. *8*. Fifty-two-year-old man with hemochromatosis, right bundle branch block. Wide splitting of second sound increased slightly on inspiration. He also had a faint apical first sound (S_1) and ventricular gallop.

*Our appreciation is expressed to Dr. Jack P. Segal, Clinical Assistant Professor of Medicine, Georgetown University Medical Center, for his permission to include this case.

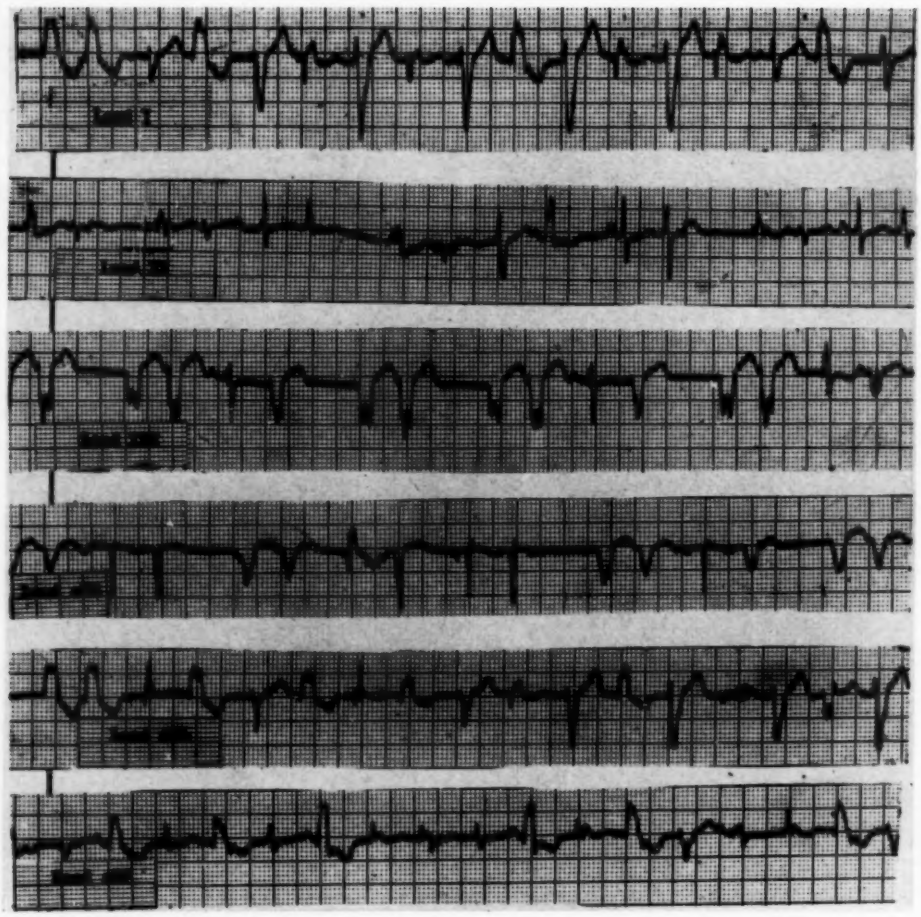

Fig. 9. A 17-year-old boy with the history of an arrhythmia which began after he had had Asian flu 2 years prior. Two days after this electrocardiogram was taken the patient died suddenly.

presence of primary myocardial disease early in its course.

Summary

The auscultatory abnormalities in primary myocardial disease have been reviewed. These abnormalities occur as manifestations of conduction defects, ectopic rhythms, myocardial failure, and associated pericarditis.

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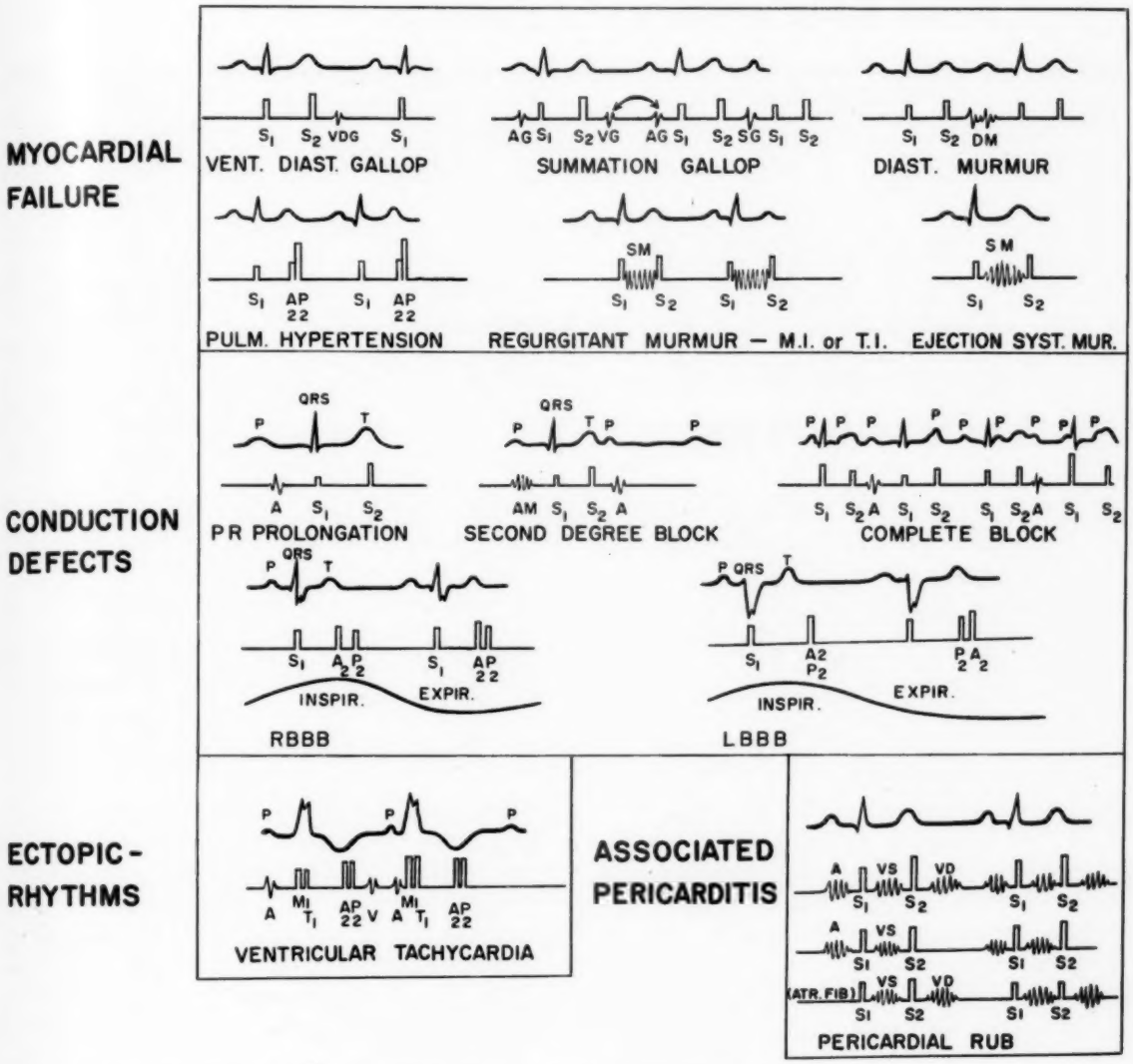

Fig. *10*. Composite of various auscultatory abnormalities in myocardial disease.

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Experimental and laboratory reports

Effects of ischemia and hypoxia on the specialized conducting system of the canine heart

Albin A. Bagdonas, M.D.
Jackson H. Stuckey, M.D.
Juan Piera, M.D.
Norman S. Amer, M.D.
Brian F. Hoffman, M.D.
Brooklyn, N. Y.

Normal cardiac function depends upon the integrity of the specialized conducting system as well as on the performances of the contractile elements. In previous studies of the effects of ischemia on the heart, emphasis has been placed on changes in the electrocardiogram and in the ability of the heart to maintain an adequate circulation during and after periods of ischemia of varying duration.[1,2] However, these studies did not show whether observed impairment of function resulted from changes in the myocardium or in the specialized conducting system. Electrical activity of the isolated heart during ischemia has been studied with intracellular microelectrodes, and changes in the transmembrane potentials of single ventricular fibers have been observed.[3] Records from the specialized conducting system, however, were not obtained. Since ischemia involves more than a lack of oxygen, the effects of interruption of the circulation would be expected to differ from those of hypoxia alone. This difference has been observed in experiments concerned with the electrical activity of isolated preparations of cardiac tissue.[3-5] Nevertheless, the terms *ischemia* and *hypoxia* often are used interchangeably.

In the present studies, the electrical activity of the intact in situ specialized conducting system has been recorded directly through multiple electrodes attached to the endocardium under direct vision during cardiopulmonary bypass. The effects of periods of ischemia which lasted 15 to 60 minutes have been compared to those which resulted from periods of moderate and severe hypoxia which lasted 60 or 120 minutes. The different results obtained from these two types of experiments suggest that ischemic changes in conduction result, in large part, from factors other than a lack of oxygen.

Method

Ten adult mongrel dogs which weighed between 20 and 30 kilograms were anesthetized with intravenous thiopental sodium, 25 mg. per kilogram of body weight. The animals were placed in the supine position, intubated with a cuffed endotracheal tube, and placed on a Jefferson respirator. The

From the Departments of Surgery and Physiology, State University of New York, Downstate Medical Center, Brooklyn, N. Y.
This work was supported in part by grants from the American Heart Association and the United States Public Health Service.
Received for publication July 1, 1960.

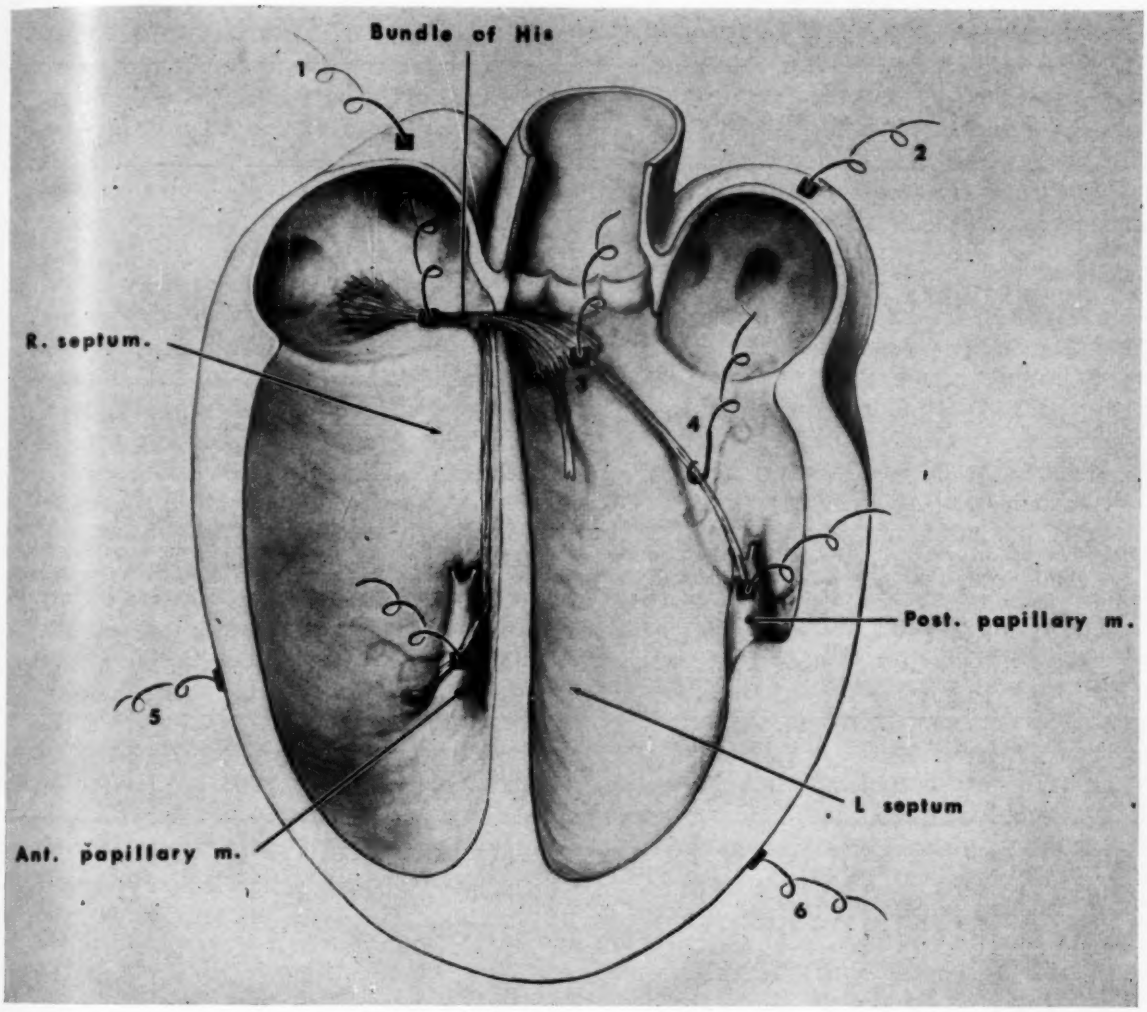

Fig. *1*. Semischematic diagram of the heart indicating the positions of the various electrodes used in the experiments. *1*, *2*, *5*, and *6* are the epicardial electrodes on the atria and ventricles, *3* is on the left bundle branch, and *4* is on the posterior free-running Purkinje fibers (false tendon) of the left bundle branch.

rectal temperature was monitored with a Tele-thermometer, and arterial blood pressure was recorded from the left femoral artery with a Statham transducer and Sanborn recorder. A standard limb lead electrocardiogram was monitored at all times and recorded in some experiments. The chest was entered transsternally through the fifth intercostal space, and the pericardium was opened widely. The azygos vein and the superior and inferior venae cavae were isolated and tapes were placed about them. The animals were then heparinized with 2.5 mg. per kilogram of body weight. Cardiopulmonary bypass was effected through an arterial cannula inserted into the right femoral artery, and venous catheters inserted into the superior vena cava via the azygos vein and directly into the inferior vena cava. A Dennis oxygenator[6] with an occlusive roller pump was used to maintain a mean arterial blood pressure of approximately 100 mm. Hg at pump flows which ranged from 70 to 100 ml. per kilogram per minute. An attempt was made to keep the rectal temperature between 37° and 38°C. by means of a Brown-Harrison heat exchanger included in the arterial circuit.

Electrodes, consisting of acrylic plaques containing 3 to 16 silver wires, 0.38 to 0.76 mm. in diameter, with the contacts separated by distances of 0.3 to 1.0 mm., were sutured to the epicardial and endocardial surfaces of the heart with No. 5-O atraumatic silk sutures (Fig. 1). The

Table I. *Conduction times—15 minutes of ischemia*

	Control	*Ischemia (min.)*								*Perfusion (min.)*				
5/29/59		1	3	4	5	7	10	12	15	1		3	28	30
A_2-H	44	54	59	—	—	—	—	—	—	—	D	91	60	53
H-LBB	11	12	10	11	12	14	14	F ⟶		F	e	11	11	11
LBB-LV	61	62	63	75	114	225	V	F ⟶		F	f	72	67	55
H-S_2	87	87	90	102	134	175	V	F ⟶		F	i	103	97	86
LBB-S_1	33	32	32	35	39	42	43	F ⟶		F	b	45	38	33
											r			
											i			
											l			
											a			
											t			
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											d			

Times are in milliseconds in all tables. In this and subsequent tables the abbreviations are as follows: A_2: Right atrium near bundle of His. H: Bundle of His. LBB: Left bundle branch. LV: Left ventricle. S_2: Septum adjacent to bundle of His. S_1: Septum adjacent to left bundle branch. F: Fibrillation. V: Variable. (–): One or both complexes absent or not suitable for these measurements (see Fig. 2).

Table II. *Conduction times—30 minutes of ischemia*

	Control	*Ischemia (min.)*												*Perfusion (min.)*						
1/27/60		1	2	3	4	5	7	8	10	12	13	20	30	1		9	13	18	28	33	38
A_1-H	52	66	39	46	63	84	207	D ⟶						D		D	65	61	55	55	54
A_2-H	44	44	44	51	60	79	223	D ⟶						D	D	D	64	59	58	57	55
H-RPPJ	24	24	22	21	22	22	23	21	21	24	F ⟶			F	e	10R	20	19	20	20	21
H-LV	64	66	63	62	68	85	136	165	151	177	F ⟶			F	f	26	60	62	62	62	63
H-S	92	93	88	83	80	83	95	95	93	95	F ⟶			F	i	38	83	87	89	90	91
P-PM	18	18	16	16	13	14	14	17	19	17	F ⟶			F	b	27	18	18	18	18	17
															r						
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Additional abbreviations: A_1: Right atrium near S-A node. RPPJ: Right Purkinje-papillary junction. S: Septum adjacent to bundle of His. P: Right Purkinje fibers. PM: Right papillary muscle. D: Dissociation. R: Retrograde conduction.

plaques were so constructed that the sutures were located 1.5 to 3.0 mm. from the actual recording site. Epicardial electrodes were placed on the right atrium near the sinoatrial node, the right and left atrial appendages, and the right and left ventricles. The right atrium was opened in all cases, and a multilead electrode was sutured over the bundle of His above the margin of attachment of the septal leaflet of the tricuspid valve. The right or left ventricle was opened, with care being taken not to injure the free-running Purkinje fibers, and an electrode was attached over the right or left bundle branch or a Purkinje-papillary junction. In one experiment, a J-shaped electrode, held manually, was used to record from the free-running Purkinje fibers. Electrograms were recorded on an eight-trace switched-beam oscilloscope (Electronics for Medicine) and photographed on 7-inch paper moving at 200 mm. per second. High- and low-pass filters in the preampli-

fiers were employed to eliminate low-frequency components of the tracer and to emphasize the electrographic deflections which result from activity of the specialized fibers.[7] If a left ventriculotomy was not performed, the left atrium was opened to avoid overdistention of the left ventricle during fibrillation. Blood from the coronary sinus was drained back to the oxygenator by means of a tube placed in the right posterolateral aspect of the chest. A thermistor was inserted into the right ventricular cavity to monitor the temperature within that chamber. In several experiments a Walton-Brodie strain-gauge arch was sutured to the ventricular wall to record myocardial contractions.

In seven experiments the effects of ischemia were studied by cross-clamping the ascending aorta for periods of 15, 30, 45, or 60 minutes. Records were made at frequent intervals during the interruption of coronary perfusion and after removal of the aortic clamp. To study the effects of hypoxia, a mixture of 50 per cent oxygen and 50 per cent nitrogen was substituted for the mixture of 97 per cent oxygen and 3 per cent carbon dioxide ordinarily used in the oxygenator. The substitution was made for a period of 120 minutes in one experiment; in two others, 100 per cent nitrogen was used for periods of 60 and 120 minutes, respectively. Again, records were made at frequent intervals during hypoxia and for 60 minutes after returning to a gas mixture of 97 per cent oxygen and 3 per cent carbon dioxide. Arterial and venous oxygen saturations were determined by the Van Slyke–Neill method before and at selected intervals during the hypoxic periods.

Results

Electrograms recorded through the electrodes located at the various sites on and within the heart were similar to those described previously.[7-11] Records obtained from the epicardial electrodes require no special description; under control conditions the configuration depended primarily on the direction of conduction with respect to the bipolar recording electrodes (see Figs. 2-6). Complexes recorded from the epicardium of the right and left atrial appendages have been designated A_1 and A_3, and those recorded from the epicardial surface of the ventricles, by V. Three major components usually were recorded through the electrodes located over the bundle of His. The first represented activity in the atrium in the vicinity of the electrode (A_2), the second, activity in the bundle of His (H), and the third, activity in the underlying interventricular septum (S or S_2). Records from either the bundle branches or the Purkinje-papillary junctions consisted of two major deflections: the first represented

Table III. *Conduction times—45 minutes of ischemia*

	Control	*Ischemia (min.)*										*Perfusion (min.)*							
	7/8/59	1	3	4	5	7	10	15	25	35	45	1	5		14	17	22	27	32
A_1-H	19	20	45	D	D	D	—	—	—	—	—	—	—	D	—	—	145R	200	85
A_2-H	35	40	61	D	D	D	—	—	—	—	—	—	—	e	B	65	—	—	49
H-RPPJ	19	19	18	20	F	→	→	→	→	→	→	F	F	f	D	D	B	B	44
RPPJ-RV	25	21	23	29	F	→	→	→	→	→	→	F	F	i	V	V	V	V	30
H-S	78	70	68	83	F	→	→	→	→	→	→	F	F	b	D	D	152	128	83
P-PM	20	17	16	16	F	→	→	→	→	→	→	F	F	r	V	V	V	V	15
														i					
														l					
														a					
														t					
														e					
														d					

Additional abbreviations: RV: Right ventricle. B: Conduction block.

Table IV. *Conduction times—120 minutes with 50 per cent nitrogen in oxygenator*

	Control	*Hypoxia (min.)*										*Oxygenation (min.)*				
10/6/59		1	3	7	15	25	45	60	90	105	120	1	5	10	21	26
A_1-H	28	32	31	5R	29	26R	28	R	R	35	35	34	35	33	35	35
A_2-H	26	26	26	13R	26	32R	25	R	R	28	28	28	28	28	30	28
H-RPPJ	18	16	17	18	17	17	13	15	15	16	19	18	18	16	15	15
H-LV	53	51	52	54	54	51	46	45	48	51	55	53	53	50	46	45
H-S	70	64	64	63	68	60	58	57	59	65	68	65	63	63	60	57
P-PM	27	25	23	24	18	18	15	15	15	17	17	17	17	17	17	16

Hypoxia was produced by a gas mixture of 50 per cent oxygen and 50 per cent nitrogen administered for 120 minutes.

activity in the specialized conducting tissue (B or P), and the second, activation of the underlying septum (S_1) or papillary muscle (M).

Over three thousand intervals between the various components of the electrograms were measured and expressed as conduction time in milliseconds. Average values are recorded in condensed form in Tables I-VI. Changes in conduction time and in electrical activity of the conducting system were studied prior to and during ischemia and hypoxia and also after a period of recovery. Although the experimental error was well below 10 per cent, only a change greater than 10 per cent in the conduction time was considered to be significant. The results are presented in two parts: (A) those obtained during ischemia, and (B) those obtained during hypoxia.

A. Ischemia. Ventricular fibrillation occurred in all experiments within 5 to 13 minutes after cross-clamping of the aorta. The atrium did not fibrillate at any time. The onset of fibrillation frequently was preceded by runs of retrograde conduction or ectopic activity which originated in the bundle branches or Purkinje system. After the aorta was unclamped, defibrillation was accomplished with one or two countershocks of 60 to 110 volts and 0.1 second duration.

Results of experiments in which ischemia lasted for periods of 15, 30, and 45 minutes are given in Tables I-III; representative electrograms for each type of experiment are shown in Figs. 2-4. During ischemia which lasted 15 minutes the earliest change noted was a progressive increase in the interval between activity in the atrium and that in the bundle of His (A_2-H), representing slower conduction in the atrioventricular node. At the same time there was a gradual decrease in the amplitude, widening and slurring of the atrial electrogram. This complex became indistinct in 4 to 5 minutes (Fig. 2 and Table I). Conduction time from the bundle of His to the bundle branch (H-LLB) or to the Purkinje system remained essentially unchanged until the onset of fibrillation after 6 to 12 minutes of ischemia. Electrical activity in the bundle of His, bundle branches, and Purkinje fibers continued during fibrillation and until the end of the ischemic period; although the electrographic complexes were diminished in amplitude in some experiments, propagated activity could be recognized. Conduction time between the bundle branch and the epicardial surfaces of the corresponding ventricle (LBB-LV) began to prolong after 3 to 5 minutes of ischemia and continued to increase until the onset of fibrillation. Even in the absence of fibrillation, electrical activity of the ventricular myocardium was difficult to identify in epicardial electrograms after 10 minutes of ischemia. There was a considerable increase in the interval between activity in the bundle of His and the activation of the underlying septum (H-S_2), and a slight increase in the interval between activity of the bundle branch and that of the underlying septum (LBB-S_1). Activity in the septum also became indistinct after 10 minutes of ischemia.

During ischemia which lasted 30 minutes the changes were similar to those described above (Fig. 3 and Table II). In the particular experiment shown in Fig. 3, the atrial electrogram gradually diminished in amplitude during the first 10 minutes

and then gradually increased during the remainder of the ischemic period, while the ventricles were fibrillating. Activity in the bundle of His became indistinct after 20 minutes, whereas activity in the Purkinje system continued throughout the ischemic period.

Ischemia which lasted 45 minutes produced no changes in conduction different from those described. Activity at the right Purkinje-papillary junction could be identified until after 35 minutes; all electrical activity was absent after 40 minutes of ischemia (Fig. 4 and Table III).

After periods of ischemia which lasted 15 and 30 minutes had been followed by a period of recovery, there was a persistent prolongation of the conduction time from atrium to bundle of His (A_1-H and A_2-H); other conduction times returned to the control values (Figs. 2 and 3 and Tables I and II). When the period of ischemia was extended to 45 minutes, a persistent prolongation of conduction time from the bundle of His to the Purkinje system (H-RPPJ) resulted. A slight persistent prolongation of the conduction time between the Purkinje system and the ventricular epicardium (RPPJ-RV) and the interval between the bundle of His and the septal myocardium (H-S_2) was recorded (Fig. 4 and Table III). During the recovery period in this experiment there was a transient 2:1 block between the atrium and the bundle of His, and also dissociation between the bundle of His and the peripheral Purkinje system.

The aorta was cross-clamped for an additional 15 minutes in the experiment of May 29, 1959 (Fig. 4), in order to compare the effects of a single 30-minute period of ischemia with those caused by two successive 15-minute periods. The additional 15 minutes of ischemia resulted in a further prolongation of the conduction time between the atrium and the bundle of His (A_2-H), and a prolongation of the interval between the bundle of His and the bundle branch (H-LBB) which persisted after defibrillation and an 18-minute period of recovery. The latter change did not occur after single periods of ischemia which lasted 30 minutes. After 45 minutes of ischemia

Table V. *Conduction times—60 minutes with 100 per cent nitrogen in oxygenator*

	Control	*Hypoxia (min.)*													*Oxygenation (min.)*					
3 2 60		1	3	4	5	8	10	15	30	35	40	45	55	60	5	10	15	20	40	60
A_1-A_3	16	15	15	15	14	14	R	R	R	8	—	—	—	—	—	—	16	18	17	18
A_1-A_2	19	15	19	18	16	16	R	R	R	28	—	—	—	—	—	—	15	16	12	3
A_1-H	56	53	52	55	55	59	R	R	R	46	—	—	—	—	—	—	D	82	79	70
A_2-H	37	36	35	37	37	40	R	R	R	73	—	—	—	—	—	—	D	67	68	67
H-RPPJ	25	25	26	26	26	25	29	36	26	25	25	E	E	E	30	25	23	23	28	25
RPPJ-RV	35	35	35	35	34	34	32	31	30	31	33	E	E	E	62	61	59	58	48	50
H-LV	65	65	66	66	64	63	66	71	57	52	56	E	E	E	68	65	60	60	60	58
H-S	83	84	86	87	83	84	87	90	74	69	73	E	E	E	93	89	86	83	82	77
P-PM	19	21	22	24	22	22	22	19	24	25	29	E	E	E	43	41	38	36	26	28

Hypoxia was produced by 100 per cent nitrogen administered for 60 minutes. E: Ectopic beats.

Table VI. *Conduction times—120 minutes with 100 per cent nitrogen in oxygenator*

	Control	*Hypoxia (min.)*													*Oxygenation (min.)*					
10 13 59		5	10	13	24	34	44	54	64	74	84	94	104	120	5	10	15	21	42	52
A_1-H	27	34	23	54R	D								—	—	D					
A_2-H	41	39	36	24R	D								—	—	D					
H-RPPJ	19	18	19	19	18	20	20	18	9R	25	25	19	31	20	25	33	31	33	30	35
H-LV	53	53	54	52	52	49	50	52	50	48	43	44	46	48	48	53	50	52	50	50
H-S	84	83	76	78	68	69	68	69	40	68	70	71	75	70	84	83	80	83	88	82
P-PM	31	31	29	29	27	30	30	28	28	32	33	25	27	28	21	37	35	36	36	22

Hypoxia was produced by 100 per cent nitrogen administered for 120 minutes.

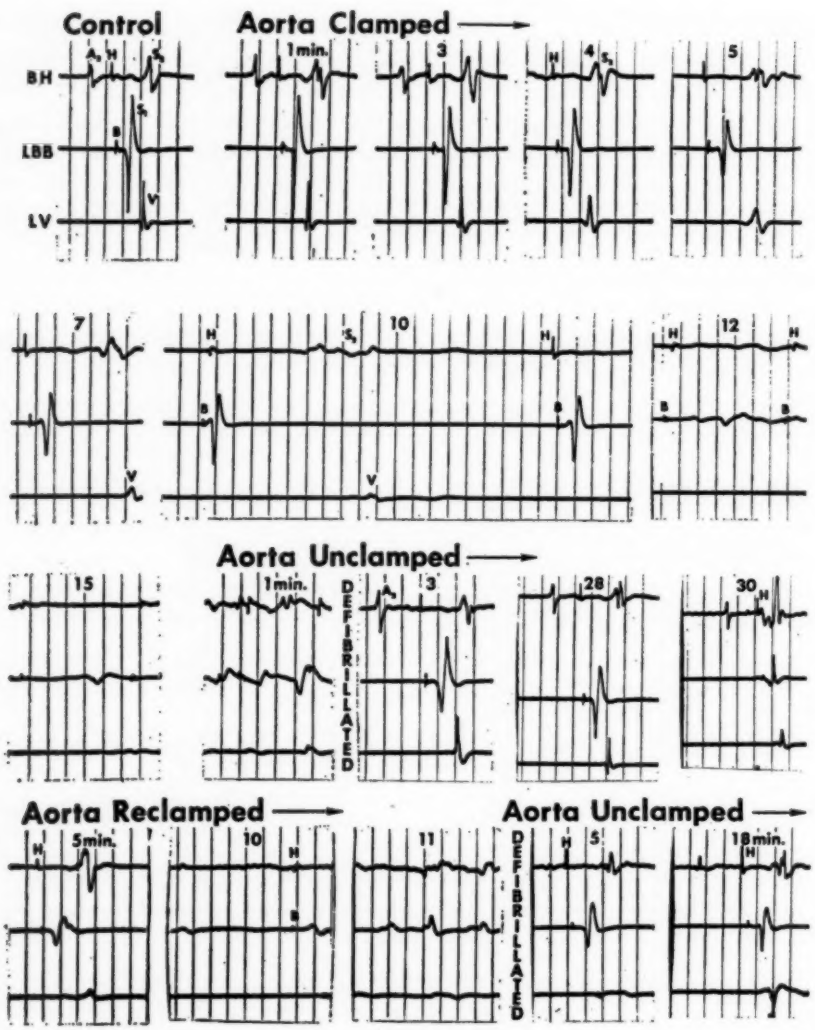

Fig. *2*. Electrograms obtained at the indicated times during two successive 15-minute periods of ischemia, each followed by a period of recovery. The electrodes are positioned as follows: bundle of His (*BH*), left bundle branch (*LBB*), and left ventricle (*LV*). The components of the electrograms are labeled as follows: A_2, right atrium; *H*, bundle of His; S_2, septum near bundle of His; *B*, bundle branch; S_1, septum near bundle branch; and *V*, ventricle. Note retrograde conduction from the bundle branch to the bundle of His, followed by a normal sequence after 10 minutes of ischemia, and ventricular fibrillation beginning after 12 minutes of the first ischemic period. In this and all subsequent records the time lines indicate intervals of 40 msec.

the aorta was cross-clamped for an additional 60 minutes. After defibrillation and 30 minutes of recovery there was no return of atrial activity, and appreciable prolongation of all conduction times persisted.

During the time that the aorta was cross-clamped, the temperature of the ventricular endocardial surfaces fell from 33°-36°C. to 30°-33°C. in 10 to 15 minutes and remained at this level until coronary perfusion was resumed. This change in temperature was not thought to make any important contribution to the disturbances of conduction described (unpublished observation of Stuckey and Bagdonas).

B. Hypoxia. Results obtained during 120 minutes of hypoxia which was produced by using a mixture of 50 per cent nitrogen and 50 per cent oxygen in the oxygenator are shown in Table IV; representative electrograms are shown in Fig. 5. Fifteen minutes after the start of the 50 per cent nitrogen mixture, the arterial oxygen saturation was 55 to 46 volumes per cent and remained in

this range until the end of the hypoxic period. The conduction time from the right atrium near the sinoatrial node to the bundle of His (A_1-H) increased while the atrium-His interval recorded from the electrode located over the bundle of His (A_2-H) remained essentially unchanged. This suggested a slowing of conduction in the right atrium. The gradual shortening of the Purkinje–papillary muscle interval (P-PM) observed during the initial 15 minutes was thought to be due to recovery from injury

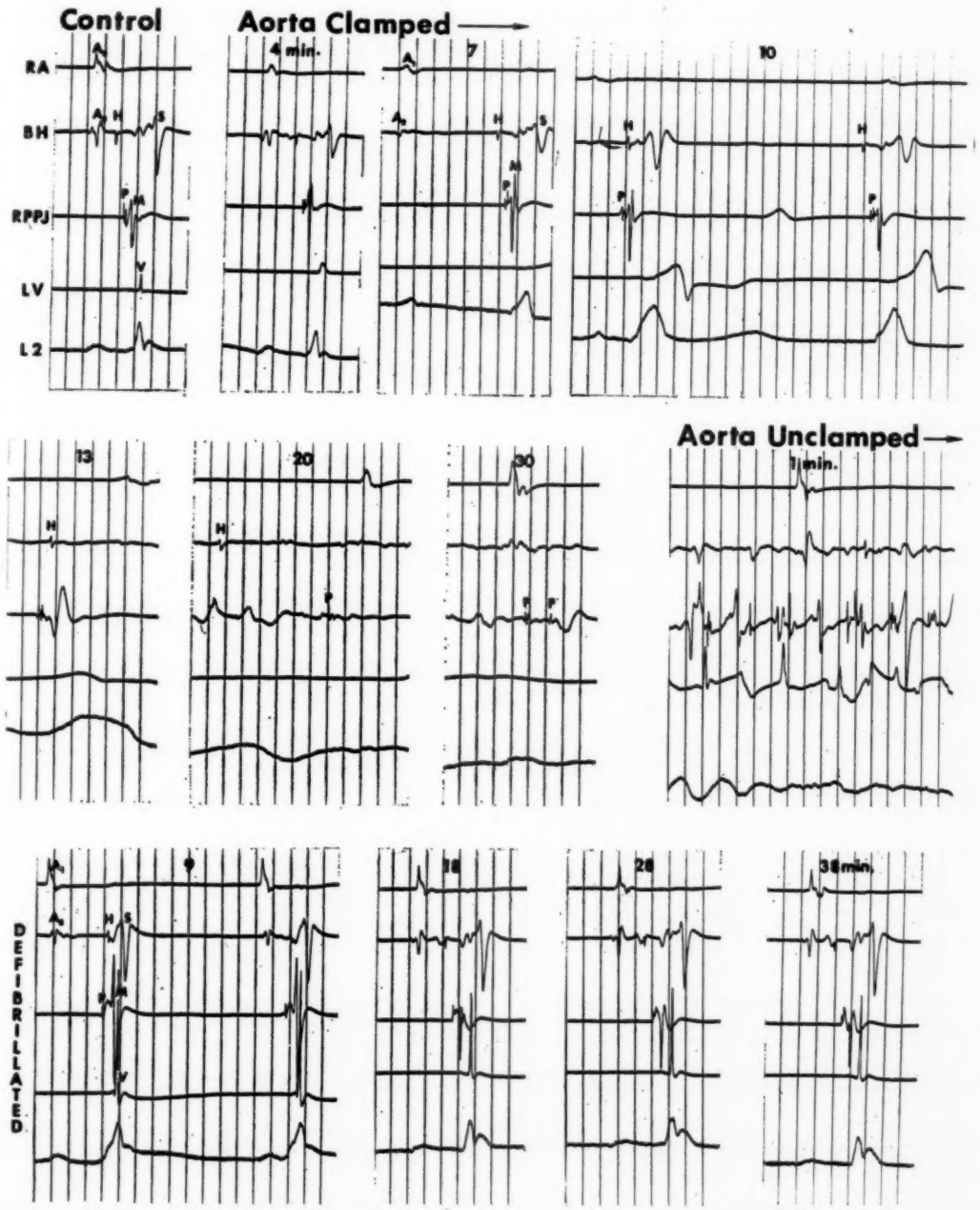

Fig. *3.* Electrograms obtained at the indicated times during 30 minutes of ischemia and during a subsequent period of recovery. Electrodes in addition to those used for Fig. 2 are positioned as follows: right atrium near S-A node (*RA*) and right Purkinje-papillary junction (*RPPJ*). *L2* designates Lead II of a standard electrocardiogram. Components of the electrograms not identified in Fig. 2 are labeled as follows: A_1, right atrium near S-A node; *S*, septum near bundle of His; *M*, right anterior papillary muscle; and *P*, activity in the Purkinje fibers. Note retrograde conduction between the bundle of His and Purkinje fibers at 10 minutes, and ventricular fibrillation at 13 minutes. Note the persistence of Purkinje activity at 30 minutes.

caused during placement of the electrode. The transient shortening of all the conduction times in the conducting system below the atrium observed at 45 minutes resulted from a temporary rise of 1.5°C. in the temperature of the body. In general, there was very little change in the conduction system during 120 minutes of moderate hypoxia. After reoxygenation, prolongation of the A_1-H conduction time persisted. The shortening of the conduction times measured in the remainder of the conducting system after 26 minutes of reoxygenation also resulted from a temporary slight rise in the temperature of the body. Left ventricular contractions, monitored with a strain-gauge arch, decreased to from one fourth to one third of the control amplitude during hy-

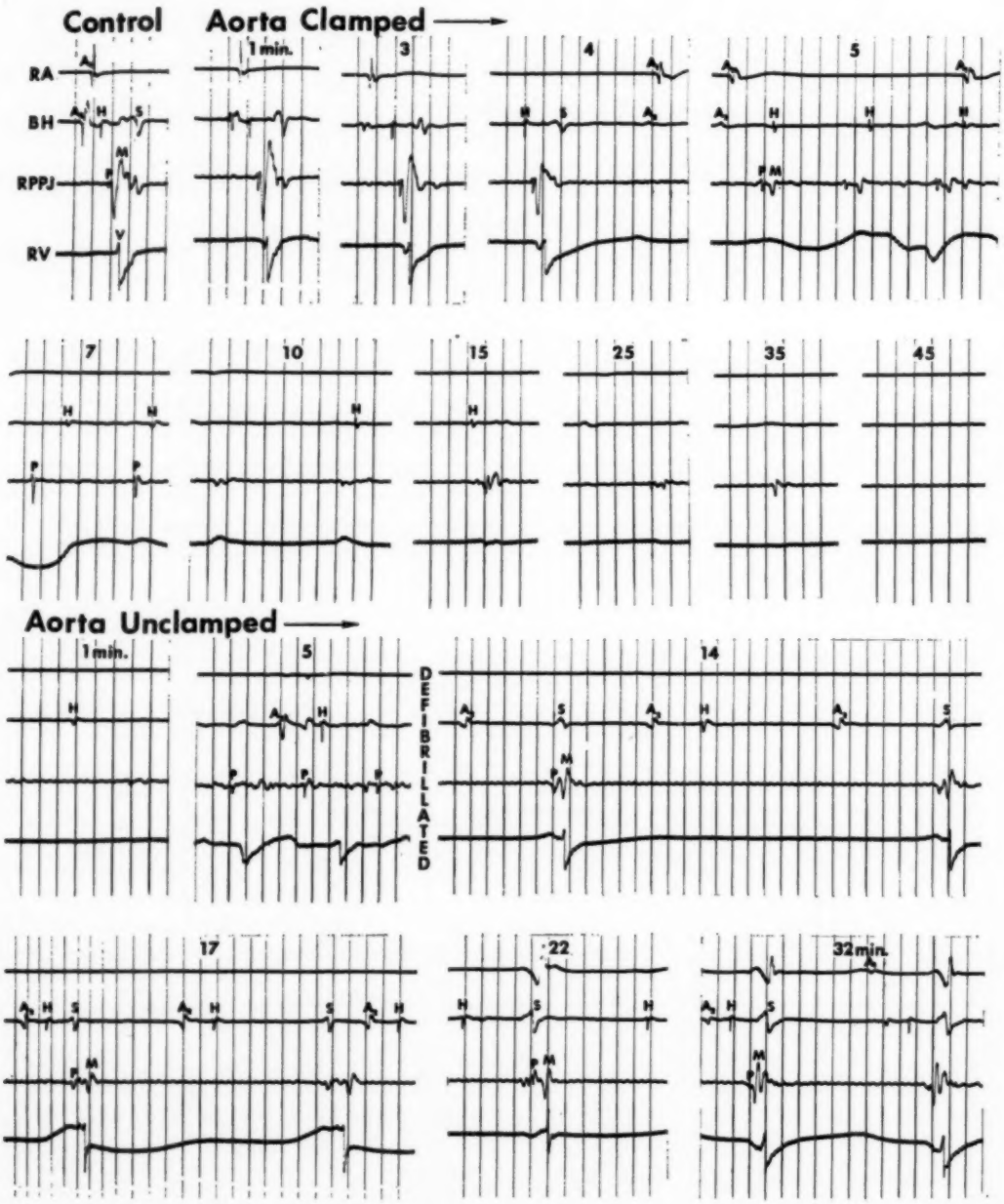

Fig. 4. Electrograms obtained at the indicated times during 45 minutes of ischemia and during a subsequent period of recovery. *RV,* Right ventricle. Note ventricular fibrillation at 5 minutes. Activity of the bundle of His persists until 15 minutes of ischemia, and activity at the Purkinje-papillary junction, until 35 minutes. During the recovery period, note the atrium-His block (2:1) and His-Purkinje dissociation at 14 minutes, and normal atrium-His conduction and continued His-Purkinje dissociation at 17 minutes.

poxia and persisted at this level after reoxygenation.

When oxygen was excluded from the oxygenator with 100 per cent nitrogen, the arterial oxygen saturation fell to 16-4 volumes per cent within 30 minutes and remained in this range during the remainder of the hypoxic period. During hypoxia which lasted 60 minutes (Fig. 6, Table V), electrical activity of the atrium gradually diminished and a nodal or His rhythm developed at 10 minutes. The retrograde activation of the atrium during nodal rhythm is indicated by the reversal of the sequence of the atrial complexes (A_1, A_2, and A_3). After 35 minutes of hypoxia, no clearly recognizable atrial activity was recorded. From 45 minutes until the end of the hypoxic period the pacemaker site probably was located in the left bundle branch or in

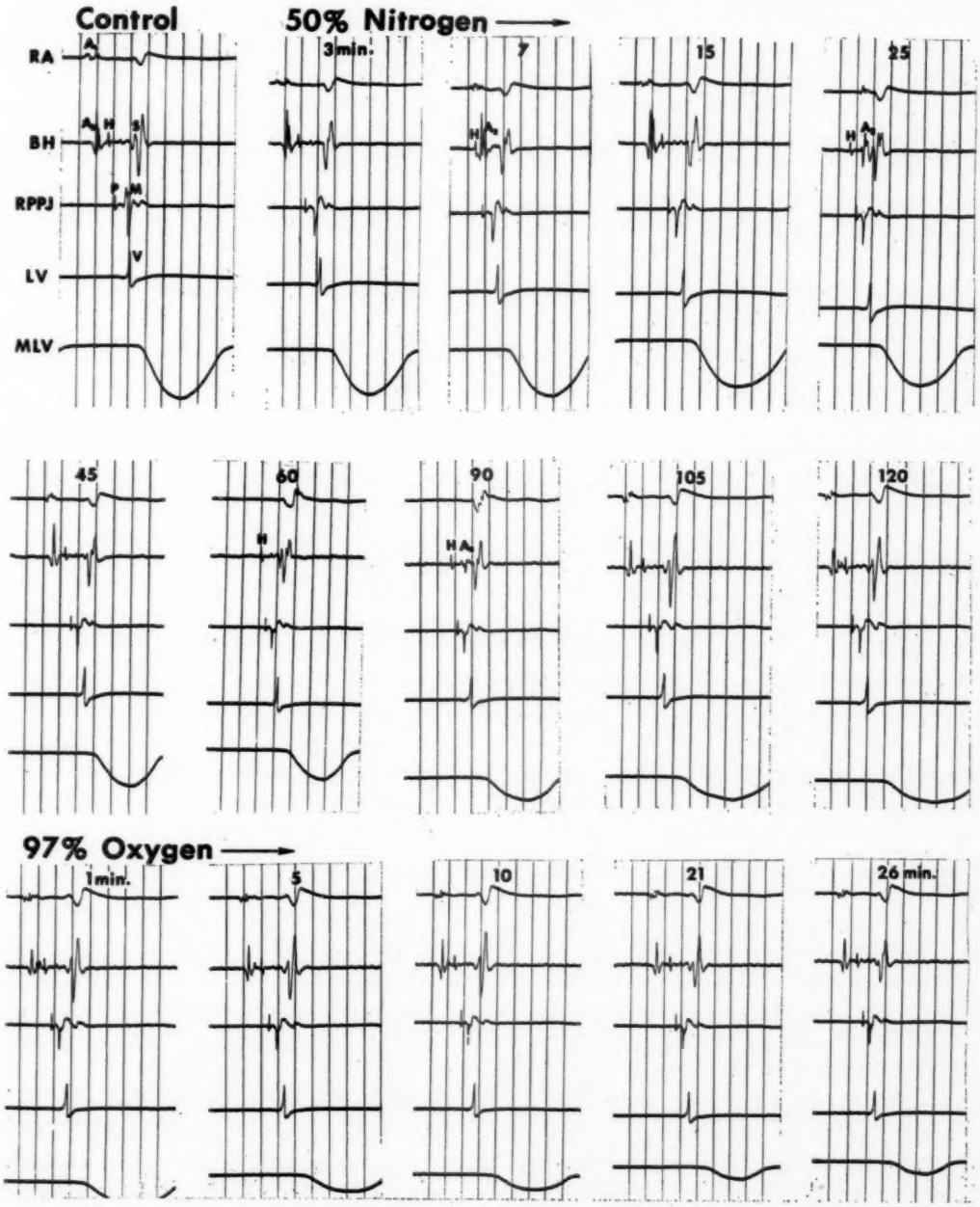

Fig. 5. Electrograms obtained at the indicated times during 120 minutes of moderate hypoxia with 50 per cent nitrogen and 50 per cent oxygen in the oxygenator, and during a subsequent period of recovery. *MLV*, Myogram recorded from the left ventricle. Note the nodal or His rhythm at 7, 25, 60, and 90 minutes of hypoxia.

the Purkinje system. Electrical activity in the specialized conducting system and in the ventricles continued until the end of the period of hypoxia, although the amplitude of the complexes was somewhat diminished. After 60 minutes of reoxygenation, there was a persistent prolongation of intervals between atrium and bundle of His (A_1-H and A_2-H), and conduction from the Purkinje system to ventricular epicardium (RPPJ-RV) and from Purkinje system to papillary muscle (P-PM) was delayed.

Severe hypoxia which lasted 120 minutes produced no additional changes. In this experiment, electrical activity of the atrium persisted through 99 minutes (Table VI). Conduction in the infra-atrial portions of the conducting system was not markedly affected during the entire hypoxic period. After reoxygenation, atrium-His dissoci-

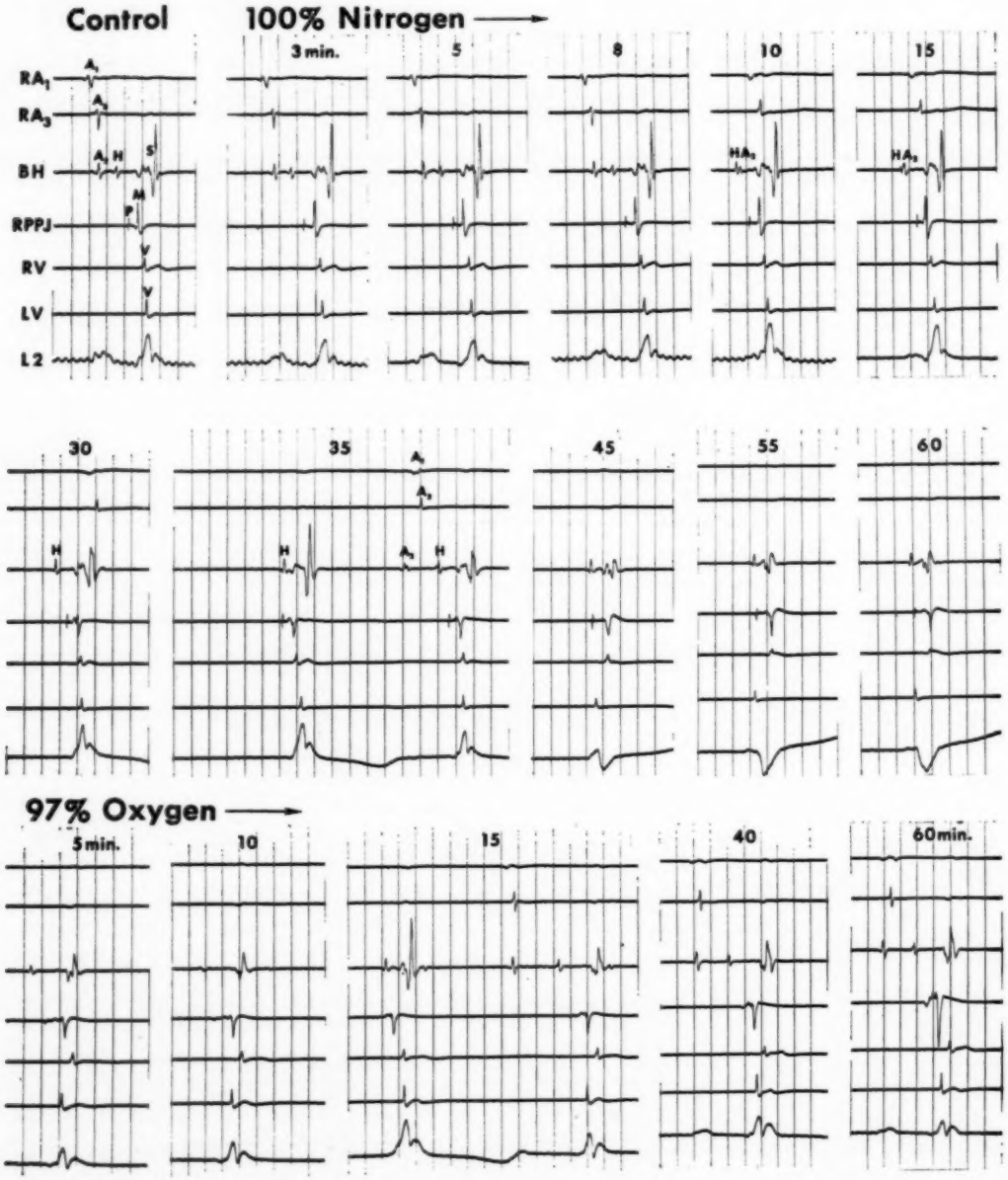

Fig. 6. Electrograms obtained at the indicated times during 60 minutes of severe hypoxia with 100 per cent nitrogen in the oxygenator and during a subsequent period of recovery. Additional electrodes are: right atrium near S-A node (RA_1), and right atrium 2 cm. from S-A node (RA_2). A_2, Activity at right atrium 2 cm. from S-A node. At the 35-minute interval, note an ectopic beat, probably originating in a Purkinje fiber, followed by a normal beat. Early activation of the left ventricle at 45 through 60 minutes of hypoxia is probably due to an ectopic pacemaker in the left bundle branch or in the Purkinje fibers within the left ventricle.

ation persisted and the conduction time from the bundle of His to the Purkinje system (H-RPPJ) became persistently prolonged. The Purkinje–papillary muscle interval (P-PM) was somewhat variable but appeared to shorten.

Discussion

Interpretation of the records obtained with the technique used in the present experiments has been discussed in previous publications.[7-11] Since interelectrode distances remained constant, the conduction times between electrodes implanted along the major conduction pathways were inversely related to the average conduction velocity. However, intervals designated by the A_2-H, LBB-S_1, and P-PM, which are recorded from a single electrode, represent differences in the time of activation of the underlying tissues and, thus, are not conduction times. In experiments of this type, the possibility of injury to underlying tissue by the electrodes must always be considered. The presence of the chronically implanted electrodes has not significantly affected either conduction through the bundle of His and the Purkinje system or the electrocardiogram during periods of observation which lasted up to 2 months (unpublished observation). In numerous experiments in which this technique is used, and which last 3 to 6 hours, no significant change in conduction has been observed.[10] One other source of experimental variation in conduction velocity must be considered, and this is the fall of 3 to 4°C. in the temperature of the heart incident to cross-clamping of the aorta. This drop in temperature is not considered to be of significance in producing any of the major changes observed during ischemia. This statement is based on experiments, in progress, on the effects of hypothermia on conduction in the specialized system. Observations made during recovery from ischemia may reflect changes due to the defibrillation which was necessary in each experiment. However, other studies[14] have shown that defibrillation by the method used in these experiments has little effect on cardiac excitability.

The interval between atrial activity recorded at the electrode over the bundle of His and activity in the bundle of His (A_2-H) is thought to be largely a measure of conduction through the atrioventricular (A-V) node and proximal bundle of His. Other studies have shown that all portions of the atrium in the vicinity of the A-V node and the bundle of His are normally activated within an interval of 5 to 10 msec.[12] If no slowing of conduction in the A-V node were present, activity in the adjacent atrium and the bundle of His would be expected to occur almost simultaneously. The fact that activity in the bundle of His occurs 35 to 60 msec. after local atrial activity (A_2) suggests that these records actually indicate the magnitude of A-V nodal delay. This interpretation suggests that the A-V node is the portion of the conducting system most sensitive to ischemia, since it was the first to be affected and the most susceptible to irreversible change.

Records of atrial activity exhibited considerable variation in conduction times and in the sequence of activation. This probably was due to shifting of the atrial pacemaker during the course of the experiment, and consequent changes in conduction pathways. In a number of experiments there was an increase in the conduction times between several electrode sites on the atrium. This, together with the fact that the amplitude of the atrial electrogram was depressed, indicates a slowing of atrial conduction during both ischemia and hypoxia.

Conduction between the Purkinje system and the ventricular epicardium (RPPJ-RV) and between the Purkinje system and the septal endocardium (LBB-S_1 and P-PM) also was quite sensitive to ischemia. However, there was no irreversible prolongation of these conduction times after ischemia which lasted as long as 45 minutes. The specialized conducting system per se, exclusive of the A-V node, was relatively resistant to ischemia, and the peripheral Purkinje system was most resistant, since it continued to fire throughout 40 minutes of ischemia and at a time when all other electrical activity had ceased.

During hypoxia the atrium and A-V node again were the most sensitive portions of the heart and specialized conducting system. When the heart was subjected to severe hypoxia for 120 minutes with arterial oxygen saturations as low as 4 per cent, the infra-atrial portion of the conduction sys-

tem was not markedly affected. These observations are consistent with physiologic studies on isolated mammalian heart tissue during deprivation of oxygen.[4,5,13]

One of the obvious differences between the effects of ischemia and those of hypoxia on cardiac conduction is that ventricular fibrillation regularly occurred with ischemia and never with hypoxia. Furthermore, recorded electrical activity was completely abolished by 45 minutes of ischemia, whereas, with the exception of the atrium, electrical activity was not remarkably affected by 120 minutes of severe hypoxia. This would suggest that a lack of oxygen alone may not be the most important factor in the production of changes observed during ischemia. Other factors, such as retained metabolites and changes in blood pH and electrolyte concentrations, may be of greater significance in affecting the conducting system. This problem is the subject of further study.

Summary

Close bipolar electrodes have been attached at selected locations on the epicardium and endocardium of in situ canine hearts during total cardiopulmonary bypass. Records from various parts of the atrium, specialized conducting system, and ventricle have been obtained during ischemia and severe hypoxia. Atrial and A-V nodal conduction were the most sensitive to ischemia and hypoxia. The specialized conducting system was least affected by ischemia, and the peripheral Purkinje system was the most resistant. Ventricular fibrillation occurred in all experiments during ischemia but was not produced by hypoxia. Recordable electrical activity was abolished after 40 minutes of ischemia. During 120 minutes of severe hypoxia, electrical activity in the atrium was depressed, whereas that in the specialized conducting system distal to the A-V node was not markedly affected.

In view of the striking differences between the effects of ischemia and hypoxia on the specialized conducting system distal to the A-V node, it is concluded that a lack of oxygen may not be so important as other factors, such as the retention of metabolites and changes in blood pH and electrolyte concentrations which occur during ischemia.

The authors gratefully acknowledge the technical assistance of Miss Anna Beck, Mr. Phillip King, and Mr. Phillip Polimeni.

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Blood flow in the calf of the leg after running

Ronald A. Livingstone, B.Sc.
Belfast, Northern Ireland

Much is now known of the effect of standardized muscular exercise on the flow of blood in skeletal muscle in man both during and after contraction. This was first described by Gaskell,[1] and later by Grant,[2] Barcroft and Dornhorst,[3] Imig and associates,[4] and many others.

Recently, Black[5] has carried out experiments after more normal forms of exercise, such as walking or running, in which he observed the behavior of the flow of blood in the calf by means of venous occlusion plethysmography. In these experiments the subjects walked or ran round a very short track, 31 yards (28.35 meters) in circumference, and maintained a standard step of 2 feet and 9 inches (83.8 cm.) by following marker lines painted on the laboratory floor. At any speed the total distance did not exceed 130 yards (118.87 M.). Within a low range of speeds (below 3.5 miles per hour; 5.6 kilometers per hour) the flow obtained immediately on cessation of exercise (peak flow) was directly related to the speed at which the exercise was taken, but the blood-debt repayment was not affected by speed. However, within a higher range of speed (above 3.5 m.p.h.) the peak flow did not increase with the speed of walking, whereas the postexercise hyperemia did. From this evidence, he concluded that vessels were capable of dilating sufficiently to meet metabolic demands during exercise up to a speed of about 3.5 m.p.h. He suggested that at this speed the dilatation of the vessels reached a maximum, and, so, at speeds above this a build-up of metabolites occurred, which resulted in a correspondingly larger postexercise hyperemia.

If this interpretation is correct, it follows that the blood-debt in the calf caused by running at speeds greater than 3.5 m.p.h. will increase as the distance run increases. If this occurs under all conditions, it is difficult to see how an athlete can run a marathon race without incurring an enormous blood-debt which might take hours or even days to repay.

In the present experiments an attempt has been made to investigate this problem by studying the postexercise hyperemia in the calf of trained and untrained subjects after they had run distances which varied from 220 yards (201.2 M.) to 8 miles (12.9 Km.) under natural conditions on an outdoor track.

Methods

Eight healthy male students, all between the ages of 19 and 25 years, acted as subjects in this series of experiments. Four of these subjects were relatively untrained in running, and 4 were prominent members of the University Athletic Club. The degree of physical fitness in the untrained subjects was fairly uniform, and not abnormally high: e.g., S.H. had not

From the Department of Physiology, The Queen's University of Belfast, Belfast, Northern Ireland.
The work described was carried out to fulfil certain requirements for admission to the Honours Degree of Bachelor of Science in Physiology in the Queen's University of Belfast, Northern Ireland.
Received for publication July 7, 1960.

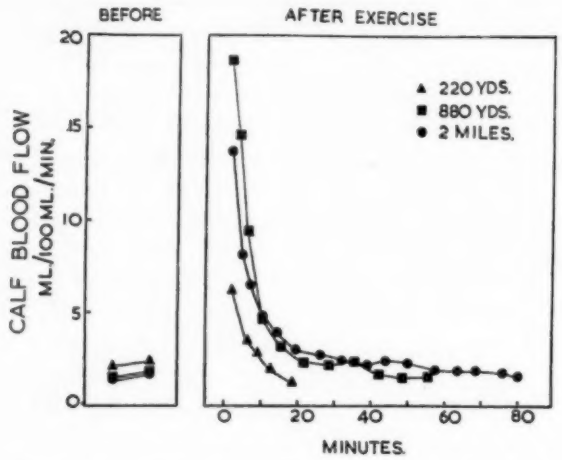

Fig. *1.* Flow of blood in calf of one untrained subject during control periods and after he had run 220 yards, 880 yards, and 2 miles at 8.5 m.p.h.

taken part in any sporting activity for some time, was of a rather studious nature, and traveled each day by bus. The athletes, on the other hand, were in the middle of their season and extremely fit.

Each subject was asked to run distances of 220 yards (201.2 M.), 880 yards (804.7 M.), and 2 miles (3.2 Km.) (on separate occasions), and each run was repeated once, so that each subject carried out six runs. The speed of the whole group was regulated to the speed which the untrained subjects could maintain over a distance of 2 miles without undue physical stress. This was found to be 8.5 m.p.h. (13.7 Km. per hour), and this speed was maintained over all distances during the experiments. In two additional experiments, observations were made on 2 trained subjects who ran distances of 6 miles (9.7 Km.) and 8 miles (12.9 Km.) at the same speed.

The subject wore singlet, shorts, socks, and running shoes, and the running was done on an outdoor circuit, 300 yards (274.3 M.) long. This was marked out in thirds, and the time at which the runner should be at each of the three points was calculated in advance. If the subject was running either too quickly or too slowly, the observer could instruct him to slow down or speed up by a prearranged system of blasts on a whistle.

The weather conditions and temperature were noted on each occasion, and the room temperature was maintained at 20 to 21° C.

Blood flows were recorded by venous occlusion plethysmography, by means of a temperature-controlled, water-filled plethysmograph[6] which was maintained at 34° C. throughout the experiment.

Since speed in obtaining the first recording after the cessation of exercise is essential, it was necessary to use a quick method of filling the inner jacket of the plethysmograph. To do this, a reservoir was prepared above the level of the head, with an emptying tube placed in the "chimney" of the plethysmograph. As soon as the subject placed his calf in the plethysmograph, the tap was opened, and the inner jacket allowed to fill while one person placed a pneumatic cuff around the ankle, and a second person a collecting cuff just below the knee. The plethysmograph was then connected up to the recording apparatus, and usually the first recording was obtained within 1½ to 2 minutes after exercise.

Procedure. For some time before the experiment the subject had taken as little exercise as possible. On arriving at the laboratory, he lay down on a couch for a period of 30 to 45 minutes. At the end of this time, two series of blood flows were taken about 10 minutes apart (10 flows in each). The average of these was taken to be the resting flow. The subject then removed his calf from the plethysmograph and began running round a circuit for the appropriate distance. The run ended at the laboratory couch, where he removed his left shoe and sock as quickly as possi-

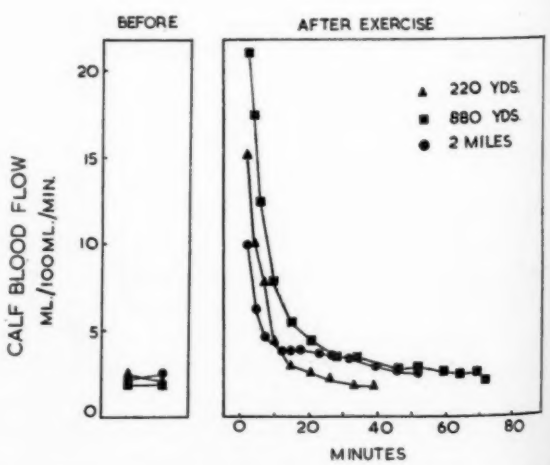

Fig. *2.* Flow of blood in calf of one trained subject during control periods and after he had run 220 yards, 880 yards, and 2 miles at 8.5 m.p.h.

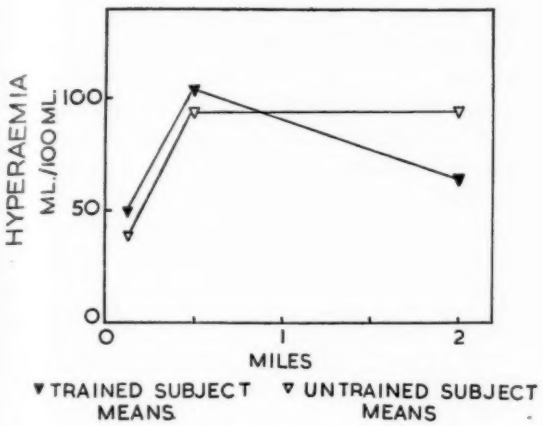

Fig. 3. Mean blood-debt repayments in trained and untrained subjects after they had run 220 yards, 880 yards, and 2 miles.

ble, and placed his left calf in the plethysmograph. Groups of five blood flows were taken, with 1-minute intervals separating the first three, then a 3-minute interval separating the third from the fourth, and subsequently the groups of flows were separated by 4-minute intervals. The experiment was continued until the flow of blood was considered to have returned to normal, as indicated by the plethysmograms.

The mean of each group of five flows was calculated, and plotted on a graph against time after cessation of exercise. The area under this curve represents the total amount of blood flowing through the calf during the period of observation. The hyperemia which resulted from the exercise is then the amount of blood flowing through the calf during this period in excess of the normal flow, which can be calculated by means of the resting values obtained at the beginning of the experiment. This value is referred to as the "blood-debt repayment."

Results

Fig. 1 shows the pattern of postexercise flows in one untrained subject after he had run 220 yards, 880 yards, and 2 miles at 8.5 m.p.h. In all cases there was a marked postexercise hyperemia which persisted for some time after exercise had ceased. The peak blood-flow reading obtained 2 minutes after the running ended showed after 220 yards a fourfold increase over the resting flow, after 880 yards an elevenfold increase, and after 2 miles an eightfold increase. The hyperemias following the three distances lasted 25, 55, and 80 minutes respectively. The total blood-debt repayment after the subject had run 220 yards was 20 ml., after 880 yards it was 114 ml., and after 2 miles it was 129.5 ml.

Fig. 2 shows the effect of running the same three distances on the flow of blood in the calf of a trained runner. The repayment after the 220-yard run was again much less than that after the 880-yard run, but in this case the repayment after the 2-mile run was only one half of that after 880 yards.

Tables I and II list the repayment values for all six runs in each of the 8 subjects. There was a considerable variation in the responses to the same stimulus from person to person, and indeed in the same individual from time to time, e.g., in M. M. the repayments after he ran 220 and 880 yards were not appreciably different on one occasion, whereas on a second occasion the repayment after he ran 880 yards was three times greater than after 220 yards.

In Fig. 3, the mean repayments after the running of each distance have been plotted for the group of untrained runners and also for the group of trained runners. It can be seen that in the untrained subjects the mean repayment increased with

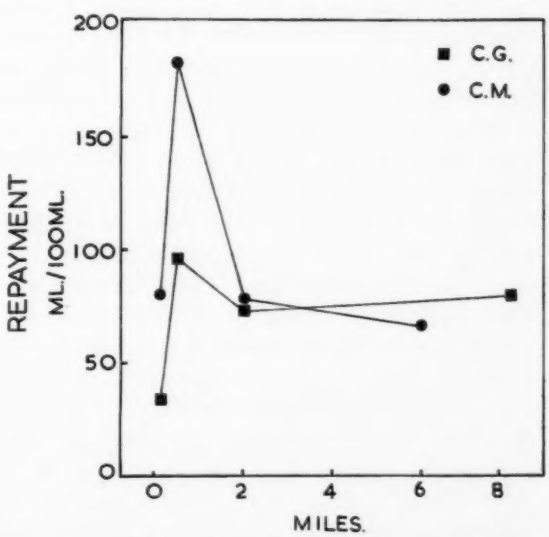

Fig. 4. Blood-debt repayments in trained subjects after they had run 6 and 8 miles. The repayments after the 220-yard, 880-yard, and 2-mile runs are also shown for each subject.

Table I. *Blood-debt repayments in 4 untrained subjects after a run of 220 yards, 880 yards, and 2 miles*

Subject	*Blood-debt repayment (ml./100 ml.)* 220 yd.	880 yd.	2 miles
J.H. (1)	20	93	93
J.H. (2)	20	110	129
J.D. (1)	55	95	106
J.D. (2)	37	85	92
M.M. (1)	42	55	100
M.M. (2)	42	121	68
S.H. (1)	25	95	95
S.H. (2)	73	98	64
Mean	39	94	94

Table II. *Blood-debt repayments in the trained subjects after a run of 220 yards, 880 yards, and 2 miles*

Subject	*Blood-debt repayment (ml./100 ml.)* 220 yd.	880 yd.	2 miles
M.C. (1)	31	37	45
M.C. (2)	20	25	68
C.M. (1)	80	182	78
C.M. (2)	56	147	74
C.G. (1)	34	96	73
C.G. (2)	40	75	40
J.D.P. (1)	92	114	72
J.D.P. (2)	52	150	69
Mean	50	104	65

distance up to 880 yards, but no further increase in repayment occurred when the distance was increased to 2 miles. In the trained subjects the mean debt repayment increased with distance up to 880 yards as before, but an increase in the distance to 2 miles resulted in a drop in repayment to near the value obtained after a run of 220 yards. A statistical analysis of all the results showed that, in the untrained group, the repayments after 220 yards were significantly less than those after 880 yards or 2 miles ($p < 0.01$), but the difference between the debts incurred by running the latter two distances was not statistically significant at the $p < 0.01$ level. In the case of the trained group the repayments after the 880-yard run, as in the untrained group, were significantly greater than those after the 220-yard run ($p < 0.01$). However, the repayments after the 2-mile run were significantly smaller than those after the 880-yard run ($p < 0.01$). The difference between the repayments after the 220 yards and the 2 miles was not statistically significant at the $p < 0.01$ level.

Fig. 4 shows the repayments measured after one trained subject ran 6 miles and another ran 8 miles, together with the repayments measured for each after the shorter distances. It can be seen that no appreciable increase in repayment occurred with this greatly increased distance; in fact, C. M. showed a slight decrease in repayment after running 6 miles.

Discussion

There is good evidence that postexercise hyperemia is caused, either directly or through an axon reflex, by the action of metabolite(s), formed during contraction, on the blood vessels of muscle.[2,7,8]

In the present experiments the calculated blood-debt repayment values after exercise probably included an increase in the flow of blood through the skin of the calf, since the form of exercise used caused a considerable amount of general body heating. In some subjects in whom the temperature of the mouth was recorded before and after exercise, it was found that the temperature of the body was raised by up to 1.7° C. after the 2-mile run, and occasionally it was raised by up to 0.5° C. after the 880-yard run. One would expect the extent of the "skin contribution" to the hyperemia to be modified by the outdoor temperature on the occasion of the experiment, and, so, a record of the outdoor temperature during each run was kept. However, a comparison of the change in temperature and the variation in hyperemic response from day to day did not reveal any obvious relationship.

The results of the experiments on the trained and untrained subjects show clearly that when the subjects were running at 8.5 m.p.h., the blood-flow repayments did not increase with distance after a critical distance had been exceeded. Indeed, in the trained runners there was a marked fall in repayment above a distance of 880 yards. This is supported by the results of the additional experiments with trained subjects, when one ran a distance of 8 miles and the other ran 6 miles. These show clearly that after 880 yards has been

exceeded, distances up to 8 miles can be run without any appreciable increase in repayment. It can be concluded from these results that while the subject is running at this speed, vasodilatation in the muscle can satisfy the increased metabolic requirements, so that a state of equilibrium is reached at which the rate of removal of metabolite by the blood stream can keep pace with its rate of formation in the muscle. In trained subjects in particular, it has been noted that the repayment after 2 miles is considerably less than after 880 yards. This could indicate an increased mechanical efficiency in the trained runner over the longer distance, or it could indicate an improved supply of blood to his calf muscle, but any attempt to produce a definite explanation of this fact on the data available would be unjustified.

A comparison of results obtained here with those obtained for walking[9] is of interest in an evaluation of the relative costs of walking and running with respect to the calf muscle. In Fig. 5 are plotted the mean postexercise repayments after walks of 880 yards and 2 miles at speeds of 3 m.p.h. (4.8 Km. per hour) and 5 m.p.h. (8.1 Km. per hour), and also those after the running of these distances at 8.5 m.p.h. The most striking feature of this diagram is that, although in walking at 5 m.p.h. there is a progressive build-up of debt with distance, no such accumulation occurs during running at a much faster speed; this difference suggests that the amount of work done by the calf muscle is less in running than in walking, although in running the over-all exhaustion of the body may be greater. This is borne out by these results, since it is clear from the diagram that the cost of running 880 yards at 8.5 m.p.h. corresponds to the cost of walking this distance at only 5 m.p.h., and the cost of running 2 miles at 8.5 m.p.h. is the same as that of walking 2 miles at between 3 and 5 m.p.h. So, although it has been found that running at this speed does not cause any progressive build-up of metabolites, running at a greater speed, if this were practicable, might lead to the metabolic requirements of the tissues outstripping the increase in the flow of blood in the calf, so that accumulation of metabolites might occur.

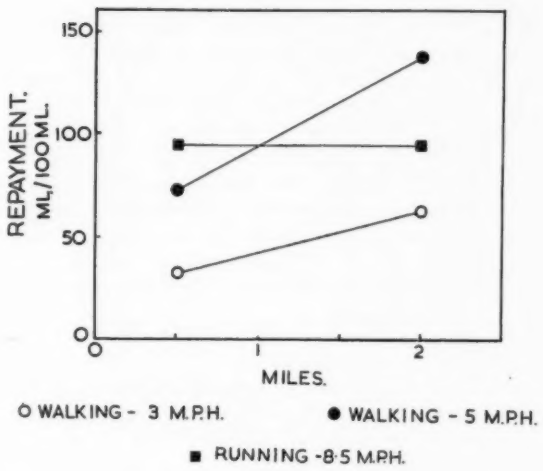

Fig. 5. Blood-debt repayments in the calf after walks of 880 yards and 2 miles at speeds of 3 m.p.h. and 5 m.p.h. are shown along with those after the running of these distances at 8.5 m.p.h. The blood-debt repayment values after the walks are taken from the results of Halliday.[9]

Summary

1. Measurements were made of the blood-debt repayments in the calf of 4 untrained subjects after they had run each of three distances, 220 yards, 880 yards, and 2 miles, at a constant speed of 8.5 m.p.h. under natural conditions on an open-air track. Similar observations were made in a group of 4 athletes.

2. A marked postexercise hyperemia occurred in both groups of subjects after all distances.

3. In the untrained subjects, blood-debt repayment increased with distance up to 880 yards and remained constant with further increase in distance.

4. In trained subjects the blood-debt repayment also increased with distance up to 880 yards, but after 2 miles it dropped to a level significantly lower than that after 880 yards.

5. Blood-debt repayments are similar after a run of 880 yards at 8.5 m.p.h. and after a walk of the same distance at 5 m.p.h.

6. It is concluded that at this speed of running there is no progressive build-up of metabolite either in trained or untrained subjects, although this does not exclude the possibility of such a build-up occurring at greater speeds.

The author wishes to thank Professor A.D.M. Greenfield, who suggested this problem, and Dr.

I. C. Roddie for his help and advice. Thanks are also due to Mr. S. J. Kilpatrick, of the Department of Social and Preventive Medicine, for his help in the statistical evaluation of the data.

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The effect of citrate infusion on the electrocardiogram of the hypothermic and normothermic dog

*James E. Doherty, M.D.**
*Masauki Hara, M.D.***
Little Rock, Ark.

The effects of hypothermia on the electrocardiogram (ECG) have been adequately described in the literature (Osborn,[1] Hicks and associates,[2] Emslie-Smith[3]); however, the effects of citrate infusion alone in hypothermic and normothermic animals and in man have received little attention. Argent[4] suggested citrate toxicity was responsible for ventricular fibrillation after massive transfusion in a human being. Ludbrook and Wynn[5] reported ECG findings of Q-T prolongation, ST-T changes, atrial asystole, and ventricular fibrillation in a patient who received a large quantity of citrated blood during hypothermia.

The present study was undertaken (1) to discover any characteristic changes in the ECG due to infusion of citrate; (2) to attempt correlation of these changes with the level of citrate in the blood; and (3) to ascertain the effect of hypothermia on these changes.

Methods

Twelve mongrel dogs were used. Each animal received acid dextrose citrate (ACD) solution buffered with sodium hydroxide to pH 7.4 at normal body temperature. About 2 to 3 weeks later, hypothermia was induced by immersion of the animal in cracked ice to a rectal temperature of about 29° C., and the infusion with ACD solution was repeated. An attempt was made to have the rectal temperature stabilized before the experiment was begun. All animals were anesthetized with thiamylal sodium and were given positive pressure artificial respiration with room air while they were hypothermic.

The rate of infusion was determined by the weight of the animal. Infusion was given at a rate of 3.45 mg./Kg./minute, a volume of 0.3 ml. per Kg./minute (7.5 ml./Kg. or 112.5 ml. total for a dog which weighed 15 kilograms). A volume of about 100 ml. of blood was withdrawn during the experiment for chemical analyses.

Specimens of blood were obtained from the inferior vena cava via a polyethylene catheter passed into the femoral vein, and arterial pressures were recorded through a similar catheter placed in the femoral artery. Recordings were performed with a Sanborn Poly-Viso 150 M recorder equipped with a Statham P23B strain gauge for determinations of pressure; the base line was adjusted to heart level. Standard electrocardiographic Leads II and III and ar-

Supported in part by a grant from the Arkansas Heart Association, U.S.P.H.S. Grant 7948-100, and National Institute of Health Grant H 3213 (C-2).
Received for publication July 11, 1960.
*Cardiologist, Consolidated Veterans Administration Hospital, and Assistant Professor of Medicine, University of Arkansas Medical Center, Little Rock, Ark.
**Professor of Surgery, University of Arkansas Medical Center, Little Rock, Ark.

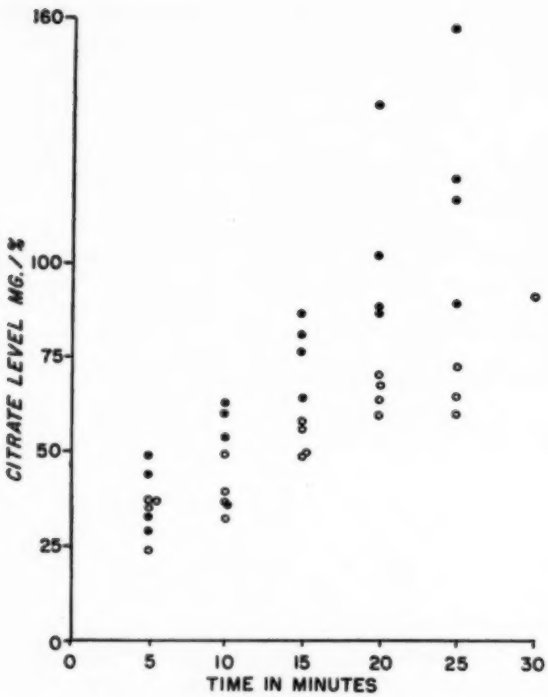

Fig. 1. Levels of citrate in the blood during normothermia and hypothermia. Solid circles represent levels of citrate in hypothermic animals, and open circles, those in normothermic animals. Rate of infusion was constant during all experiments. Note uniformly higher figures obtained with hypothermia.

terial pressure (25 mm./sec. paper speed) were recorded at the same time that blood was being obtained for analysis. A control observation was made before each experiment, and specimens were obtained and recordings were made every 5 minutes for 25 minutes during infusion of the ACD solution. The specimens were analyzed for blood citrate, calcium, pH, and total protein. The calculations of ionizable calcium were determined by a process of successive approximations, using the nomograms of MacLean and Hastings.[6,7]

Analysis of data

Serial specimens obtained at 5-minute intervals during normothermia and hypothermia were analyzed for blood citrate. Consistently higher levels were observed in hypothermic dogs when comparison was made with the levels in normothermic controls. A graph demonstrating this reduction in citrate metabolism during hypothermia is shown in Fig. 1.

Electrocardiographic changes induced by hypothermia (29°C. rectal temperature) were: characteristic "Osborn" waves,* ST-T changes, and prolonged atrioventricular and intraventricular conduction time which have been previously described.[1-4] The infusion of citrate tended to produce (1) more Q-T prolongation than did hypothermia alone, and (2) an electrical alternans of the T wave. This latter change was not detected by us when hypothermia was used alone. The mechanism of this abnormality is not apparent, although it is probably associated with a change in myocardial metabolism.

The "alternating T" change was seen one time during infusion of citrate into a normothermic animal. This suggests that this may be an electrocardiographic change associated with administration of citrate exclusive of hypothermia.

Three types of "alternating T" changes were observed and are shown in Figs. 2 and 3.

The following is a useful qualitative descriptive classification of the T-wave changes observed. *Type I:* Alternating T wave consisting of a slight lowering of the T wave in every other complex (marked with Roman numeral I over arrow at 25 minutes in Fig. 3,*A*). *Type II:* Alternating T wave showing every other T wave more deeply negative (marked in Fig. 2 with Roman numeral II). This is the most frequently observed variety. *Type III:* Alternation of the T wave with one complex exhibiting a flat or biphasic T wave and the second complex showing a negative wave (marked Roman numeral III in Fig. 2).

It was felt that a more comprehensive description of the T alternans would include many subtypes which might be confused with changes ordinarily seen in hypothermia alone.

A summary of the data obtained on 4 representative animals is presented in Table I and Figs. 3 and 4. There would appear to be little correlation between the appearance of T alternation and any change observed, except the level of citrate in the blood. T alternation appeared with a fair degree of consistency at a level of approximately 70 mg. per cent of citrate in the blood of the hypothermic animals. Dog No. 8 (Table I and Figs. 3 and 4) failed to exhibit any T

*An early diastolic wave first described during hypothermia by J. J. Osborn[1] and shown in Fig. 2.

alternation, however, in spite of levels of 83.2 mg./100 c.c. Dog No. 7 (Table I and Figs. 3 and 4) exhibited marked T-wave changes while hypothermic, and slight T-wave changes under normothermic conditions.

A fall in mean blood pressure was observed during infusion of ACD into hypothermic animals, and often when T-wave alternans appeared, an alternating pressure curve was observed as well (Fig. 4). Very close inspection will reveal a slight QRS alternans at times; however, this is not noticeable in most of the observations. Dog No. 8 exhibited fairly noticeable hypothermic changes in the electrocardiogram but failed to exhibit T alternans attributable to the administration of citrate. Dog No. 10 revealed marked T alternation during hypothermia. None of the other 8 animals exhibited any T alternation during normothermia. During hypothermia, all exhibited T alternation of the types shown in Figs. 2, 3, and 4.

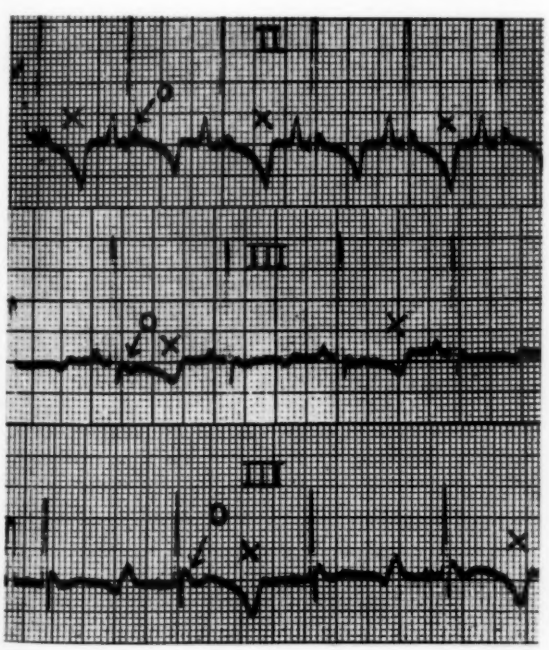

Fig. 2. Electrocardiograms demonstrating three examples of T alternation observed during hypothermia and infusion of citrate. All traces demonstrate early diastolic Osborn waves (marked *O*) usually seen in hypothermia, as well as T alternans. Complexes showing the more deeply negative alternate T waves are marked *X*. Type-II and Type-III changes described in text are marked. Changes of this magnitude were observed with levels of blood citrate of 50 mg. per cent and above, usually 70 mg. per cent and above. These examples were all selected from animals after 25 minutes of infusion of ACD, with levels of blood citrate of 90 mg. per cent or more.

Other experiments in this laboratory[8] have indicated that no consistent alternation in the serum potassium is observed during ACD infusion of this type, and this determination was not performed in the present study.

Changes in blood pH are known to produce marked changes in the electrocardiogram, and some of the observed effects may reflect subtle changes in pH attendant on the administration of ACD. It is noted, however, that little correlation exists between changes in the blood pH and the electrocardiographic changes observed during the experiments (Table I). The blood pH of the dogs was generally higher when they were hypothermic than when they were normothermic. During infusion of ACD, however, the pH was not observed to be consistently higher or lower than the control determination. We feel that the differences in pH may be explained by differences in ventilation, since the ACD solution was buffered to normal serum levels.

Animals rendered hypothermic exhibit a general slowing of body metabolism. This results in a similar reduction in the metabolism of most drugs administered during the hypothermic state, as has been demonstrated for citrate (Fig. 1). Hypothermia is similarly responsible for slow cardiac rates and hypotension.

T alternation was usually accompanied by a prolongation of the Q-T interval (see Table I), and this finding was demonstrated in all of the animals in this study, except 2. Fig. 5 is a graph which illustrates the relationship of the Q-T interval to the level of citrate in the 4 representative experiments described previously. Note that an increase in the Q-T interval usually accompanies a rise in the level of citrate in the blood, and the averages of increases in Q-T interval during infusion, when plotted against the level of citrate for both hypothermic and normothermic animals, produced curves that are significant in normothermic animals to $p = 0.025$ and in hypothermic animals to $p = 0.010$ (linear regression). The most pronounced effect on the Q-T interval is observed in the hypothermic group. The

Table I

		Dog No. 7						Dog No. 8					
Time (min.):		*Control* 0	5	10	15	20	25	*Control* 0	5	10	15	20	25
P–R (sec.)	N	0.08	0.09	0.08	0.08	0.075	0.08	0.12	0.11	0.09	0.10	0.09	0.10
	H	0.13	0.12	0.12	0.12	0.12	0.16	0.12	0.13	0.12	0.12	0.12	0.13
QRS (sec.)	N	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.05	0.05	0.05	0.05	0.05
	H	0.08	0.07	0.08	0.07	0.06	0.06	0.07	0.08	0.07	0.07	0.07	0.07
Q–T (sec.)	N	0.26	0.26	0.24	0.24	0.25	0.27	0.28	0.24	0.25	0.26	0.25	0.24
	H	0.43	0.44	0.54	0.56	0.54	0.60	0.30	0.32	0.32	0.32	0.33	0.33
Rate per min.	N	150	154	165	160	162	155	120	140	140	150	150	155
	H	96	94	90	92	96	75	144	145*	145*	140*	140*	142*
Mean pressure (mm. Hg)	N	126	126	115	120	115	120	120	100	50	45	25	55
	H	65	50	40	35	20	15	135	125	115	115	110	115
Citrate (mg. %)	N	4.0	37.0	49.6	57.6	70.4	90.4	2.8	35.6	32.0	56.0	67.2	72.0
	H	3.2	49.2	60.0	81.6	148.8	160.8	1.2	28.0	36.0	64.8	83.2	83.2
Calcium (mg. %)	N	9.8	—	9.5	—	10.1	—	7.8	—	10.8	—	7.9	—
	H	10.8	—	10.2	—	10.5	—	11.5	—	10.1	—	9.9	—
Ionized calcium (mM./L.)	N	1.00	0.72	0.48	0.40	0.38	0.34	0.49	0.32	0.18	0.14	0.17	0.14
	H	1.00	0.40	0.47	0.38	—	—	1.45	1.05	0.69	0.58	0.42	0.42
pH	N	7.5	—	7.55	—	7.55	—	7.5	—	7.5	—	7.5	—
	H	7.7	—	7.6	—	7.65	—	7.5	—	7.55	—	7:55	—
Total protein (Gm. %)	N	6.8	—	7.0	—	7.0	—	4.9	—	4.4	—	4.5	—
	H	8.3	—	7.3	—	6.6	—	5.5	—	5.4	—	5.0	—

*Pressure curve damped.
N: Normothermic. H: Hypothermic.

Table I—Cont'd

		Dog No. 10						Dog No. 12					
Time (min.):		*Control* 0	5	10	15	20	25	*Control* 0	5	10	15	20	25
P–R (sec.)	N	0.10	0.08	0.08	0.08	0.09	0.10	0.08	0.09	0.08	0.09	0.08	0.08
	H	0.14	0.12	0.12	0.12	0.14	0.16	0.12	0.13	0.13	0.14	0.14	0.14
QRS (sec.)	N	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
	H	0.07	0.06	0.07	0.06	0.08	0.08	0.06	0.06	0.07	0.08	0.08	0.06
Q–T (sec.)	N	0.17	0.22	0.21	0.21	0.20	0.22	0.20	0.22	0.20	0.20	0.22	0.24
	H	0.33	0.32	0.36	0.40	0.46	0.48	0.35	—	0.38	0.39	0.44	0.46
Rate per min.	N	130	160	162	160	155	150	150	155	160	160	160	170
	H	106	108	100	90	80	82	120	130	115	110	104	100
Mean pressure (mm. Hg)	N	145	145	120	120	110	110	120	160	150	150	155	150
	H	110	105	100	75	70	60	120	120	115	110	85*	80*
Citrate (mg. %)	N	1.6	36.0	39.0	49.6	64.0	60.0	3.6	24.0	37.6	48.8	59.2	64.0
	H	2.4	44.4	63.2	80.0	102.0	121.6	6.4	33.6	54.0	76.0	86.4	116.0
Calcium (mg. %)	N	11.6	—	11.4	—	10.0	—	12.4	—	12.2	—	11.1	—
	H	11.2	—	10.7	—	10.8	—	13.4	—	13.0	—	13.2	—
Ionized calcium (mM./L.)	N	1.4	0.84	0.80	0.70	0.50	0.50	—	—	—	—	—	—
	H	1.41	0.99	0.61	0.50	0.52	0.38	1.41	0.99	0.61	0.50	0.52	0.38
pH	N	7.45	—	7.5	—	7.5	—	7.4	—	7.4	—	7.4	—
	H	7.6	—	7.6	—	7.6	—	—	—	—	—	—	—
Total protein (Gm. %)	N	6.1	—	5.5	—	5.5	—	6.1	—	5.8	—	5.5	—
	H	5.5	—	4.9	—	4.6	—	6.7	—	6.6	—	6.0	—

*Pressure curve damped.
N: Normothermic. H: Hypothermic.

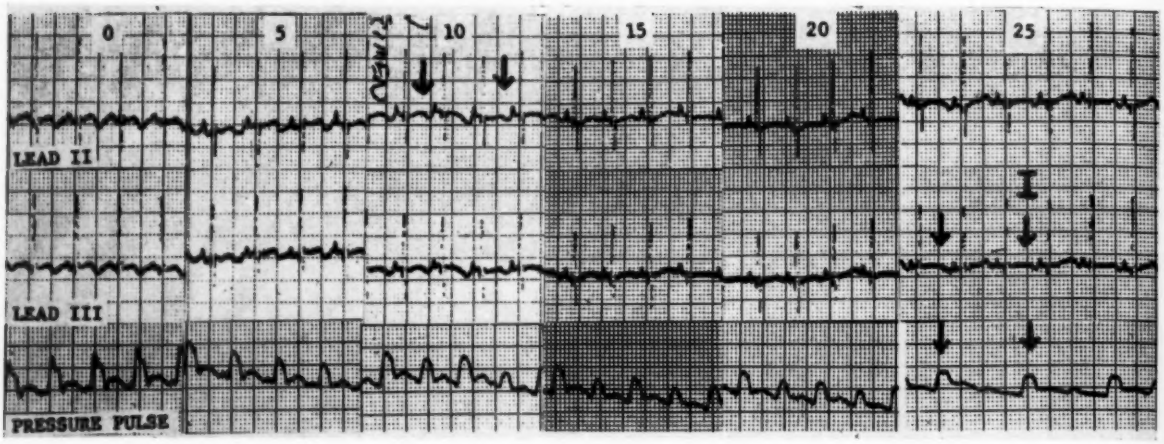

Fig. 3. Representative experiments in 4 normothermic dogs. ECG Leads II and III and simultaneous pressure pulse. Pulse waves are shown for contour only; for exact determinations of pressure see Table I. Time in minutes is shown at the top of each figure. *A*, Dog No. 7 demonstrates T alternans while normothermic during infusion of citrate. The best ECG example of alternation is seen at 10 min.; pulse contour alternans appears at 25 min. These changes are designated by arrows. *B*, Dog No. 8. Note lowering of T wave in all ECG tracings subsequent to the control. Pulse contour is badly damped. *C*, Dog No. 10. Little change in the ECG is seen during entire experiment. Pulse contour tends to change with a fall in mean blood pressure. *D*, Dog No. 12. Very slight T changes (no alternans) are observed. Pressure pulse contour is damped at 25 min.

Q-T measurements were not corrected for rate, because the usual formulas for correction of the Q-T interval are not particularly applicable at the fast and slow rates observed in these experiments. The effect of hypothermia alone in the production of the slow rate might account for the control observation of the prolonged Q-T interval; however, since the body temperature remained relatively constant, further prolongation which occurred during the infusion of ACD may be taken as an effect of the infusion.

The effect of the infusion of ACD on serum calcium was of interest, since citrate is known to depress the plasma ionized calcium. Unfortunately, no generally satisfactory method is available for the determination of ionized calcium, and one must rely upon the calculated figures shown in Table I. Generally, values of ionized calcium are lower during hypothermia and infusion of ACD; however, Dog No. 8 demonstrates that this finding was not consistent. Infusion of ACD did, however, depress the ionized calcium to values below control levels in every instance, including Dog No. 8, in which T alternation was not detected. We conclude that the levels of ionized calcium or of serum calcium do not correlate well with the appearance of T alternation seen in our experiments.

Discussion

The electrocardiographic demonstration of T alternans was of greatest interest to us, since we had not seen such a striking T change without the more common type of electrical alternans involving the QRS complex. Close inspection of the tracings presented here will reveal slight degrees of QRS alternans; however, this change is not so readily apparent as the changing T wave. As with the QRS type of alternans, the pulse wave occasionally exhibited this alternating phenomenon (Fig. 4). T alternans has apparently been produced to a lesser degree through the administration of tri-iodothyronine. The possibility of alteration of the transmembrane potential in some fashion which renders the cell (or cells) more or less permeable to certain ions has been suggested as a hypothesis to explain this phenomenon; however, the metabolites and the exact mechanisms involved are obscure.[9]

There is a paucity of information in regard to the effect of various drugs administered under hypothermic conditions in animals and in man. Hypothermia does cause an over-all reduction in bodily function at almost every level, and administered substances tend to accumulate more rapidly because of ineffective metabolism and/or excretion. Fisher and associates[10] have

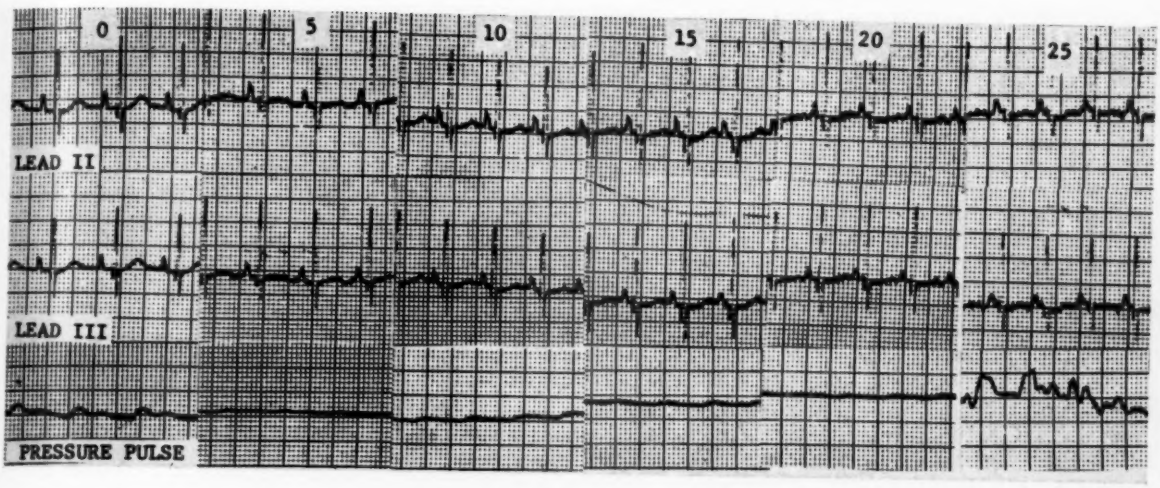

Fig. *3,B.*

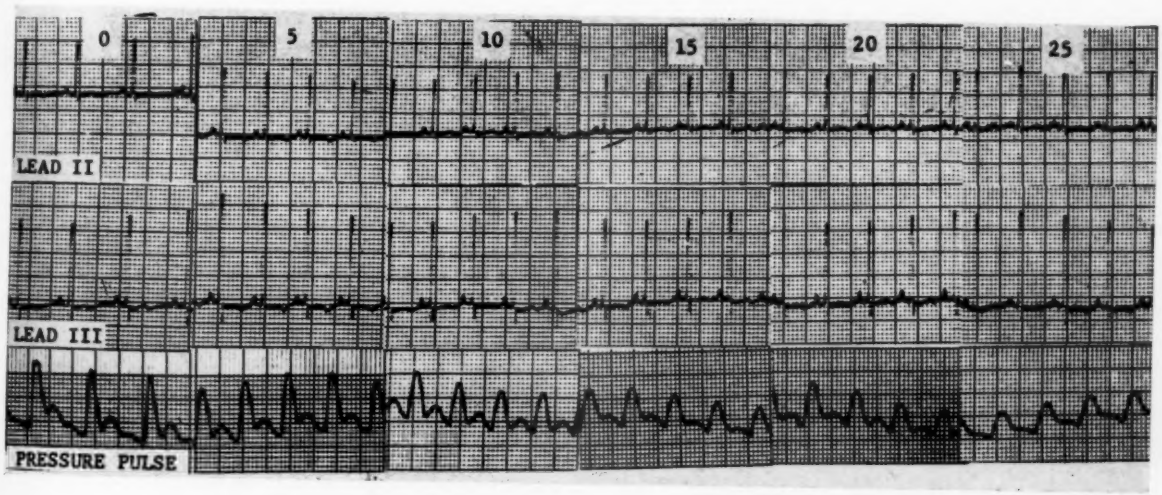

Fig. *3,C.*

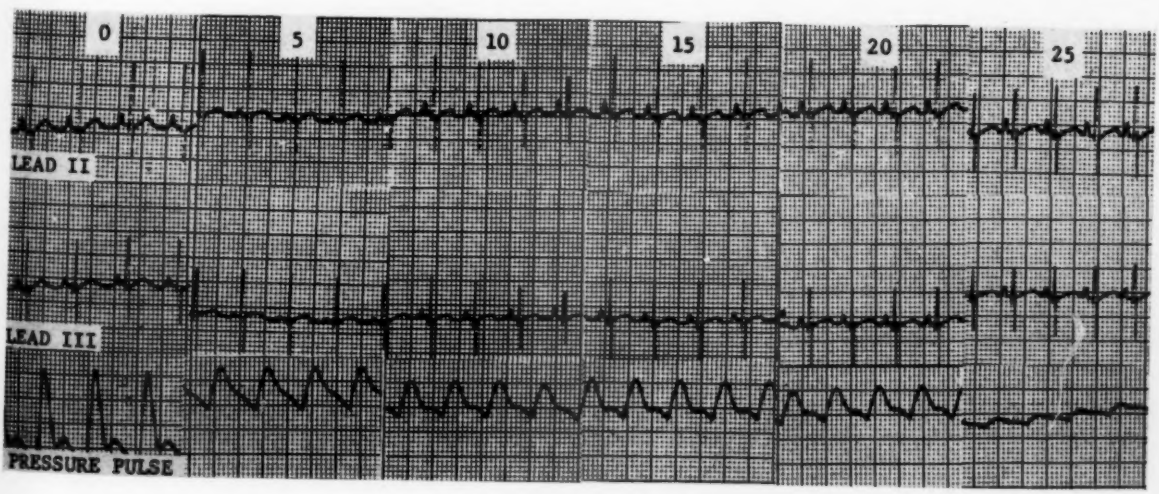

Fig. *3,D.*

(Legend for Fig. 3, B, C, and D on opposite page.)

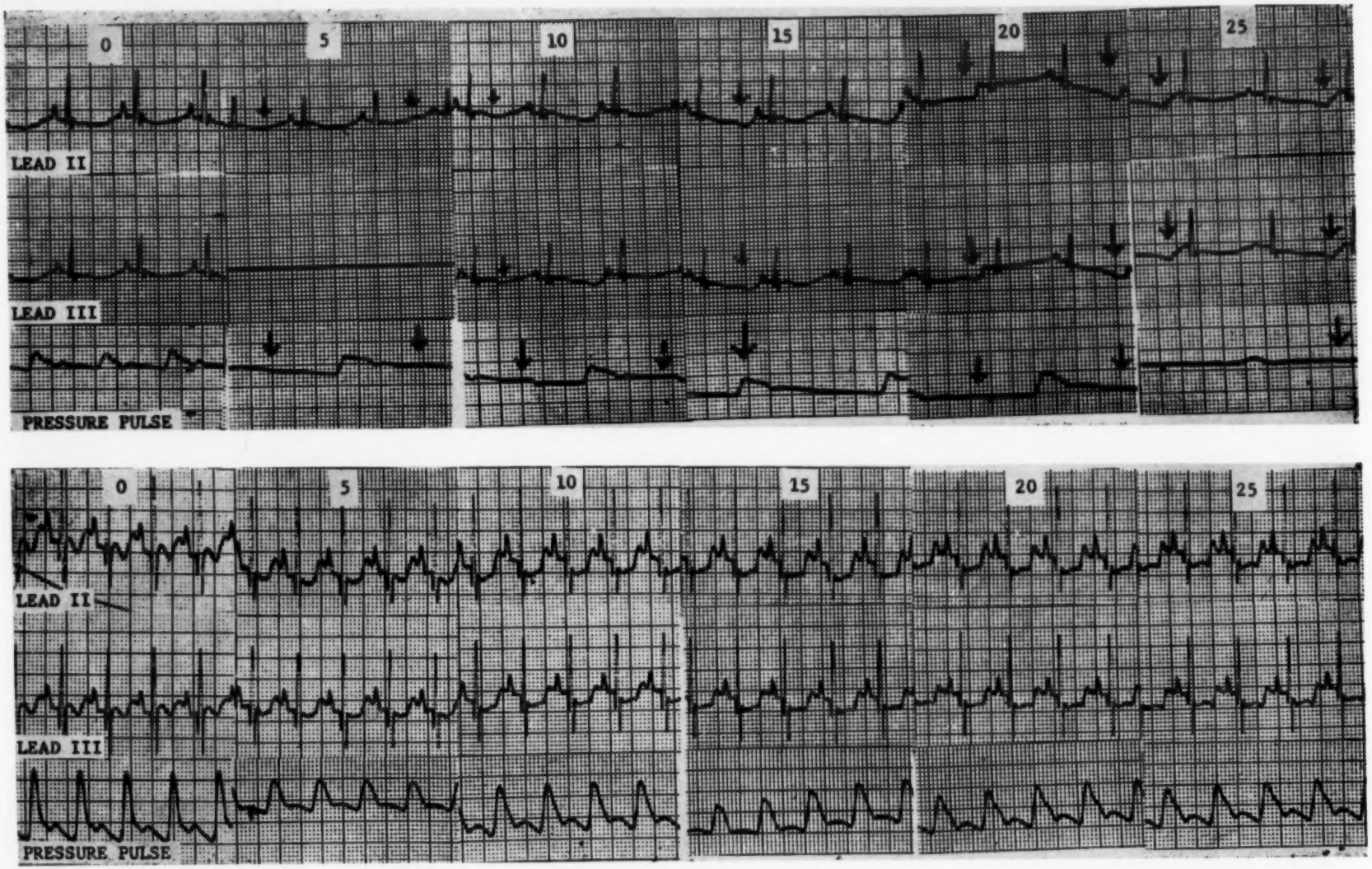

Fig. 4. *A-D*, Representative experiments in 4 hypothermic dogs. ECG Leads II and III and simultaneous pressure pulse. Pulse waves are shown for contour only; for exact determinations of pressure see Table I. Time in minutes is shown at top of each figure. ECG and pulse pressure changes are designated by arrows. *A*, Dog No. 7. Control ECG shows typical hypothermic changes. Lead III at 10 min. could not be recorded because of technical difficulty. Note T alternans in all ECGs recorded during infusion and pressure pulse alternation. Type-II changes throughout infusion. *B*, Dog No. 8. Note marked Osborn waves, ST-T changes, and (somewhat unusual) tachycardia on control tracing. Although additional ST-T changes occurred during infusion, T alternans of the types usually seen did not appear during this experiment.

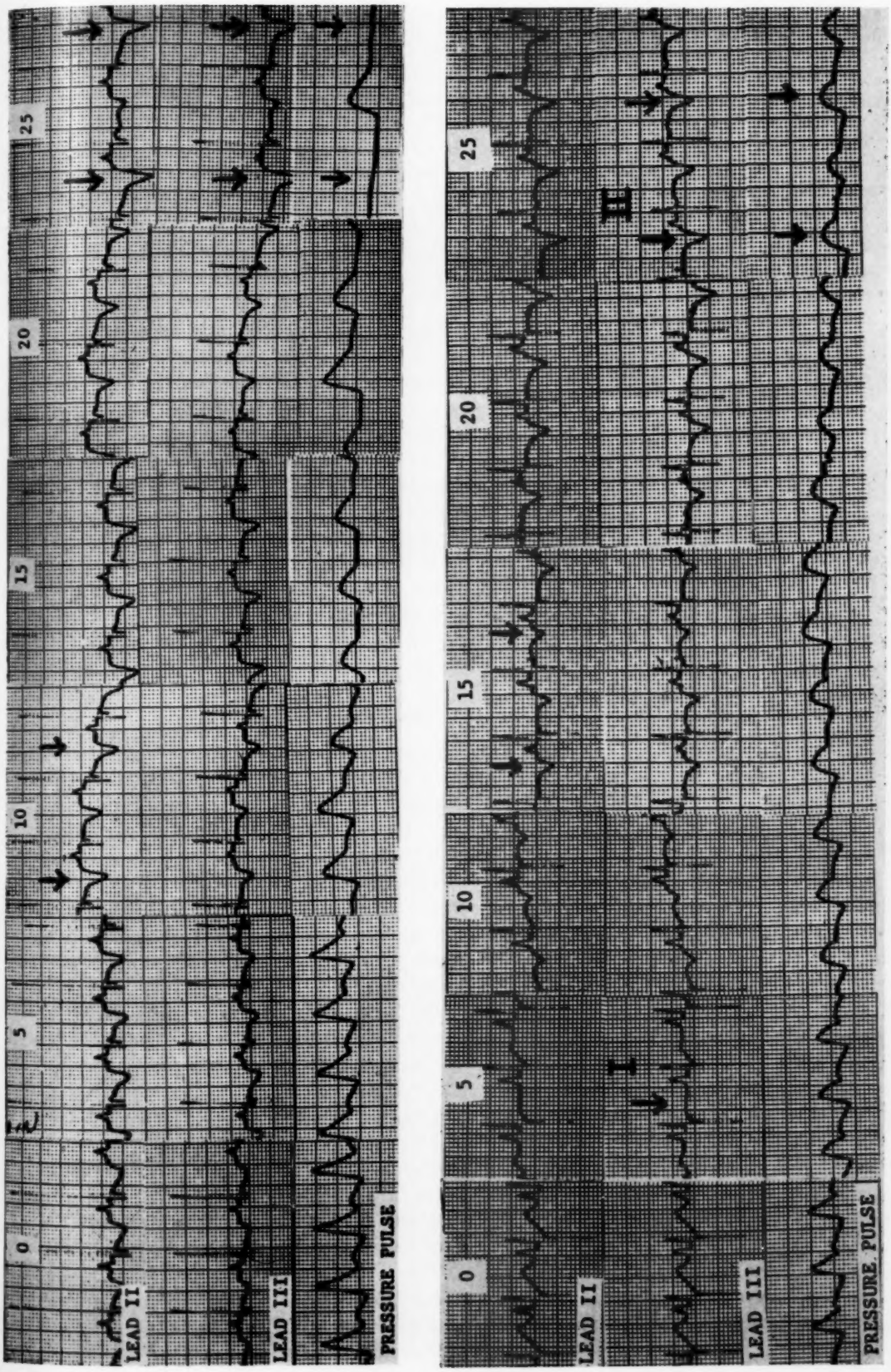

Fig. 4—Cont'd. *C*, Dog No. 10. T alternans appears at 10 min. Pulse contour alternation is detected at 20 min. Type-II changes throughout. *D*, Dog No. 12. Marked ST-T changes throughout. Type-I T alternans begins at 5 min. Successive tracings reveal Type-II changes, seen from 10 through 25 min. Pulse wave alternans is seen only at 25 min.

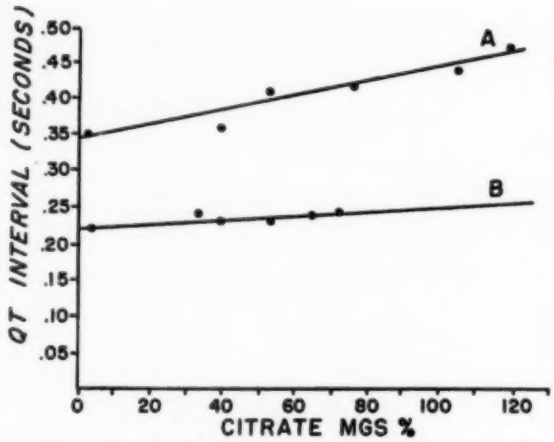

Fig. 5. The effect of the infusion of citrate on the Q-T interval in normothermic and hypothermic dogs. Curve *A* represents an average of the Q-T intervals and levels of citrate in 4 hypothermic dogs annotated in Table I and Figs. 3 and 4. Curve *B* represents the same calculations in these dogs under normothermic conditions. Note the initial higher levels and more profound effect of citrate on the Q-T interval in the hypothermic animal. These curves are statistically significant by linear regression. The Q-T interval is not corrected for rate because the comparison of the tachycardia and bradycardia associated with barbiturate anesthesia and hypothermia, respectively, makes the usual formulas inapplicable. The feature that is of most interest, however, is that the infusion of ACD causes proportionately more prolongation under hypothermic than normothermic conditions.

noted the depressant effect of hypothermia on the functioning of the liver. This undoubtedly plays a large part in the apparent decrease in tolerance to, or increased effect of, substances detoxified or modified by the liver which were administered during the hypothermic state. Hubbard and associates[11] report a case of severe citric acid intoxication occurring during an infundibular resection because of a tetralogy of Fallot. Their patient developed hypotension and electrocardiographic changes after receiving 750 c.c. of citrated bank blood over a 20-minute period. These changes were apparently corrected through administration of calcium. Inspection of their illustration reveals Type-I T alternans during administration of the citrated blood.

It is also of interest to speculate that the changes of T alternation observed may represent changes in the U wave rather than intrinsic changes in the T wave. The appearance of early T-wave changes as well as late changes would seem to make this less likely but still a possibility.

Boba[12] has stated that a peculiar early diastolic wave (Osborn wave) is related to the appearance of ventricular fibrillation during hypothermia. All of the hypothermic tracings reproduced here demonstrate the Osborn wave, and we have not been impressed with its value in predicting the onset of ventricular fibrillation. We are certain, however, that this wave is present in most of the animals rendered sufficiently hypothermic for the induction of ventricular fibrillation. Our electrocardiographic experience with hypothermia leads us to conclude that there are no characteristic changes which precede ventricular fibrillation, and that the Osborn or early diastolic wave is not an ominous sign.

One of the authors (J.E.D.) had the opportunity of monitoring the electrocardiogram on a patient under hypothermia for operation on an aneurysm of the circle of Willis. Massive hemorrhage led to the rapid (5-minute) infusion of 1,000 ml. of citrated bank blood. Type-II alternans of the T wave was induced. The patient subsequently recovered without sequelae.

Summary

Data have been presented which demonstrate changes in the electrocardiogram of normothermic and hypothermic dogs during the intravenous infusion of buffered ACD solution.

The most striking change was an electrical alternans of the T wave which occurred in varying degrees, but which was present in all animals except one under hypothermia. Osborn waves, and P-R, QRS, and Q-T prolongation were also demonstrated. Normothermic animals demonstrated slight Q-T prolongation and T-wave lowering, rarely a modest form of T alternans.

The possibility exists that the electrocardiographic T alternans was a result of a reduction in the level of the ionized serum calcium; however, the data presented neither support nor disprove this hypothesis.

The T alternans described was noted to occur in a human patient under hypothermia and rapid transfusion. It is not an ominous sign and was not associated with increased mortality during animal experiments or in the human subject mentioned above.

The authors gratefully acknowledge the technical assistance of Marilyn H. Lile, M.T., and wish to express thanks to Mr. Fred Jungkind for the photographic reproduction of graphs and electrocardiograms, and to Dr. S. William Ross for assistance in calculation of ionized calcium.

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A prong-catheter for inducing vascular distention in the intact animal

Clark M. Blatteis, Ph.D.
Eugene F. Tucker
Fort Knox, Ky.

In cardiovascular research it is sometimes desired to study the effects in the intact animal of localized vascular distention. The preferred method at present consists of passing a Dotter-Lukas (balloon) catheter to the experimental site,[1-3] and then to inflate the balloon. The difficulty arises, however, in that the inflated balloon obstructs the flow of blood, making interpretation of results obtained by this method disputable.

The present communication describes a new instrument for distending blood vessels without obstructing flow.

Methods and results

The device consists of 4 pieces of staggered lengths, circa 1-3/4 inches, of .022-inch spring steel wire soldered onto a .045-inch spring steel wire which runs the entire length of a 50 cm., size 10F, radiopaque Cournand catheter (Fig. 1). These 4 wires are bent outward so as to form a spreader approximately 1½ inches in diameter, which retracts into a tube 2¼ inches long made from ¼-inch brass tapered on both ends externally and threaded onto the outer diameter of the catheter. The tube is counterdrilled ½

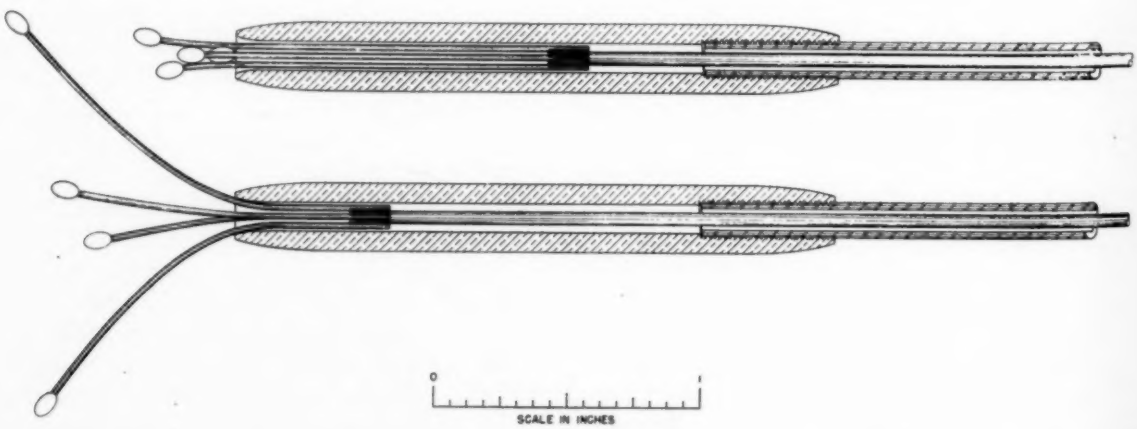

Fig. 1. Engineering diagram of the prong-catheter. *Above:* Spreader retracted. *Below:* Spreader expanded.

From the Division of Environmental Medicine, U. S. Army Medical Research Laboratory, Fort Knox, Ky.
Received for publication July 18, 1960.

Fig. 2. X-ray photograph of the prong-catheter expanded in the inferior vena cava, near its entrance into the right auricle. The other catheters have been positioned in the chambers of the heart for the recording of pressure.

inch on its proximal end to accommodate a 6/32-inch tap, so that it cuts its own thread when screwed onto the catheter but not deeply enough to damage it. The tips of the wires have small knobs of solder to prevent them from puncturing the walls of the blood vessel when expanded. The proximal end of the long wire has a handle for grasping.

The catheter is ready for insertion into a vessel when the wires are retracted into the tube. By pushing forward on the handle, the prongs are released distally and the vessel is distended (Fig. 2).

Conclusions

The above-described instrument shows promise of very practical usefulness in cardiovascular research since it is possible to position the catheter in any desired, accessible area of the vascular tree, permitting local mechanical vascular distention without the inconvenience of blocking the flow of blood. We have found this device useful in studies involving the afferent initiation of the Bainbridge reflex. These will be reported in a separate publication.

Summary

A new prong-catheter is described that permits vascular distention in the intact animal as a tool for studying certain cardiovascular reflexes.

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The systemic and coronary hemodynamic effects of 1-(2-methoxyphenol)-4-(3-methoxypropyl)-piperazine phosphate

George G. Rowe, M.D.
Cesar A. Castillo, M.D.
Hans P. Gurtner, M.D.
Skoda Afonso, M.D.
Carl J. Chelius, M.D.
Charles W. Crumpton, M.D.
Madison, Wis.

An antihypertensive drug which has recently been made available is 1-(2-methoxyphenol)-4-(3-methoxypropyl)-piperazine phosphate* (Ansiv), also known as Abbott HT 1479. It has been shown to lower the blood pressure of both normotensive and hypertensive experimental animals and to produce slight changes in coronary blood flow as measured by Morawitz cannula or Langendorff perfusion.[1] Since the agent has some clinical promise, a pharmacologic study in experimental animals was undertaken in order to elucidate its hemodynamic effects in more detail.

Material and methods

The study was done in 10 mongrel dogs which varied in weight between 18 and 30 kilograms. The animals were anesthetized by 3 mg. per kilogram of morphine sulfate given subcutaneously and followed in 1 hour by intravenous administration of 0.25 ml. per kilogram of a 50/50 mixture of Dial-urethane and veterinary pentobarbital.* After anesthesia was secured, cardiac catheters were maneuvered fluoroscopically into the pulmonary artery, the right atrium, and the coronary sinus, and Cournand needles were placed percutaneously in each femoral artery.

Cardiac output was determined by the direct Fick principle, and expired air was collected via a cuffed endotracheal tube and a Tissot spirometer. Gas analyses were done by the Van Slyke–Neill method on blood specimens and by the Scholander method on expired air. Coronary flow was determined by the nitrous-oxide saturation method. The nitrous-oxide analyses were made by the method of Orcutt and Waters. The pH was determined on whole blood by means of the Cambridge model R pH meter. In 9 animals, during the determination of cardiac output by the Fick principle and again during the measurement of coronary blood flow, cardiac output was also

From the Department of Medicine and the Cardiopulmonary Research Laboratory, University of Wisconsin, Madison, Wis.

This work was supported in part by grants from the National Heart Institute, U. S. Public Health Service, the Wisconsin Alumni Research Foundation, and the Wisconsin Heart Association.

Received for publication July 20, 1960.

*Dial-urethane, furnished by the courtesy of CIBA Pharmaceutical Products, Inc., Summit, N. J., contains Dial 100 mg./ml., monoethylurea 400 mg./ml., and urethane 400 mg./ml. Veterinary Nembutal contains 60 mg./ml. of sodium pentobarbital.

determined by the Hamilton indicator-dilution method, using the Gilford model 103 IR densitometer and indocyanine green as the indicator substance. The indicator was injected into the pulmonary artery, and sampling was done from the femoral artery, with a constant withdrawal pump set to withdraw at a rate of 25 c.c. per minute. Each curve was calibrated by using known concentrations of indicator in whole arterial blood from the dog under study. The indicator-dilution curves, pressure curves, and electrocardiogram was recorded by the Gilson direct-writing macropolygraph. Statham strain gauges were used for all pressures, and the mean pressures were determined by electrical integration. Standard formulas were used for all calculations.

After control determinations the animals were given either 0.5 or 1 mg. per kilogram of Ansiv rapidly into the pulmonary artery or coronary sinus (one half of the animals received each dose); approximately 20 minutes subsequent to the administration of Ansiv, the second determination of the cardiac output was made and was followed by determination of coronary flow.

Results

Results of the study are summarized in Table I. It will be seen that there was a significant increase in cardiac rate (+54.0 per cent, $p < 0.01$) accompanied by a significant decrease in mean blood pressure in the systemic and pulmonary arteries. Right atrial pressure decreased in 9 out of 10 animals. The minute volume of respiration increased significantly (+37 per cent, $p < 0.05$), and there were slight but significant increases in both the consumption of oxygen and the elimination of carbon dioxide. The respiratory quotient also increased slightly. On the other hand, the arterial and mixed venous oxygen contents as well as the arteriovenous oxygen difference remained unchanged. Apparently associated with the increased ventilation,

Table I. *Hemodynamic effects of HT 1479*

Parameter	*Control ± SEM*	*Drug ± SEM*	*% Change*	*p Value <*
Cardiac rate	87 ± 7	134 ± 13	+54.0	0.01
Mean systemic arterial blood pressure (mm. Hg)	112 ± 4	93 ± 3	−17.0	0.01
Mean pulmonary arterial blood pressure (mm. Hg)	15 ± 2	13 ± 2	−13.3	0.05
Mean right atrial blood pressure (mm. Hg)	3.0 ± 0.3	1.5 ± 0.7	−50.0	0.1
Volume respiration (L./min.)	2.7 ± 0.2	3.7 ± 0.5	+37.0	0.05
Oxygen consumption (ml./min.)	107 ± 7	115 ± 8	+ 7.5	0.05
Carbon-dioxide elimination (ml./min.)	87 ± 6	98 ± 7	+12.6	0.01
Body respiratory quotient	0.80 ± 0.01	0.86 ± 0.02	+ 7.5	0.05
Arteriovenous oxygen difference (ml./100 ml. blood)	4.7 ± 0.4	4.6 ± 0.4	− 2.1	0.8
Mixed venous carbon-dioxide content (ml./100 ml. blood)	50.6 ± 1.0	47.5 ± 1.1	− 6.1	0.001
Venoarterial carbon-dioxide difference (ml./100 ml. blood)	3.5 ± 0.3	3.8 ± 0.4	+ 8.6	0.6
Coronary sinus oxygen content (ml./100 ml. blood)	4.3 ± 0.6	3.2 ± 0.4	−25.6	0.05
Arterial coronary sinus oxygen difference (ml./100 ml. blood)	11.7 ± 0.5	13.2 ± 0.6	+12.8	0.05
Coronary sinus carbon-dioxide content (ml./100 ml. blood)	55.3 ± 1.1	53.0 ± 1.3	− 4.2	0.05
Arterial coronary sinus carbon-dioxide difference (ml./100 ml. blood)	10.2 ± 0.5	11.4 ± 0.5	+11.8	0.01
Cardiac respiratory quotient	0.88 ± 0.03	0.87 ± 0.03	− 1.1	0.8
Arterial hematocrit reading	43 ± 1	43 ± 2	—	—
Arterial pH	7.24 ± 0.01	7.25 ± 0.02	+ 0.1	0.2
Coronary sinus pH	7.21 ± 0.02	7.22 ± 0.02	+ 0.1	0.5
Cardiac output (L./min.)	2.5 ± 0.3	2.7 ± 0.2	+ 8.0	0.6
Stroke volume (ml.)	30 ± 4	21 ± 3	−30.0	0.01
Total peripheral resistance (c.g.s. units)	4,038 ± 498	2,912 ± 253	−27.9	0.02
Total pulmonary resistance (c.g.s. units)	515 ± 67	414 ± 85	−19.6	0.1
Left ventricular work (Kg.M./min.)	3.8 ± 0.5	3.4 ± 0.4	−10.5	0.2
Right ventricular work (Kg.M./min.)	0.5 ± 0.1	0.5 ± 0.1	—	—
Coronary blood flow (ml./100 Gm./min.)	87 ± 6	83 ± 4	− 4.6	0.6
Cardiac oxygen usage (ml./100 Gm./min.)	10.0 ± 0.5	10.9 ± 0.8	+ 9.0	0.4
Coronary vascular resistance (units)	1.33 ± 0.09	1.14 ± 0.07	−14.3	0.2
Index of efficiency	0.38 ± 0.04	0.32 ± 0.03	−15.8	0.1

there was a decrease in the mixed venous and arterial carbon-dioxide content, with an unchanged mixed venous-arterial carbon-dioxide difference. The oxygen content of coronary sinus blood decreased significantly (−25.6 per cent, $p < 0.05$), with a significant increase in the arterial coronary sinus oxygen difference (+12.8 per cent, $p < 0.05$). Although the carbon-dioxide content of coronary sinus blood decreased (−4.2 per cent, $p < 0.05$), it decreased less than did the arterial carbon-dioxide content, with the coronary sinus–arterial carbon-dioxide difference increasing significantly (+11.8 per cent, $p < 0.01$). The cardiac respiratory quotient was unchanged. Neither the arterial hemoglobin nor the hematocrit changed significantly in the experimental, as compared to the control, observations. When the control observations were compared with the experimental observations, there were no significant changes in pH in the femoral arterial or in the coronary sinus blood.

Cardiac outputs as determined by the indicator-dilution method averaged 0.3 L. per minute less than those determined by the Fick principle. This difference was statistically significant ($p < 0.01$). Hence, those outputs measured by the Fick principle are used in the table and in the calculations. Comparison of the cardiac outputs determined by the Hamilton method first during the determination of the cardiac output by the Fick principle and again during the determination of coronary blood flow showed no significant difference between these determinations. There was an average difference between these two determinations of only 0.1 L. per minute, indicating a fairly steady state throughout the procedure.

There was no difference in cardiac output in the control as compared to the experimental period, whether the figures derived from the Fick or those from the Hamilton methods are compared. Central blood volume, as calculated from the Hamilton indicator-dilution curves, indicate a slight but insignificant reduction after the administration of Ansiv. Total peripheral resistance was reduced (−27.9 per cent, $p < 0.02$), and left ventricular work decreased slightly (10.5 per cent) but not significantly. There were no significant differences in coronary hemodynamics, although coronary blood flow tended to decrease (−4.6 per cent, $p < 0.6$), as did coronary vascular resistance, whereas myocardial oxygen usage per 100 grams tended to increase.

Discussion

The search for desirable antihypertensive drugs continues, with one of the goals an agent which will reduce peripheral vascular resistance so as to permit the hypertensive subject to maintain normal blood flow at a lower systemic arterial pressure. Hydralazine is such an agent, since it produces hypotension accompanied by increased cardiac output,[2] and increased cerebral,[3] renal,[4] and coronary blood flow.[5] The ganglion-blocking group of drugs,[6-8] and chlorothiazide,[9,10] insofar as information is available, have produced hypotension chiefly through decreasing cardiac output. It is of considerable interest then for a hypotensive agent to reduce blood pressure without decreasing cardiac output, as Ansiv has done in this study. These results are of greater interest since cardiac output was maintained in spite of reduced venous filling pressure in 9 of the 10 animals. This may indicate that the administration of Ansiv is associated with a more favorable "Starling performance curve," although in the absence of data concerning end-diastolic pressures in the two ventricles this cannot be determined as defined by Sarnoff.[11] When the calculated external efficiency of the heart is compared before and after the administration of Ansiv, the amount of work done per unit of oxygen consumed is actually slightly less (−15.8 per cent, $p < 0.1$). This may well be related to the cardiac acceleration which accompanied the administration of the drug in these animals, since cardiac acceleration is known to affect efficiency adversely.[12] At the same time it should be pointed out that coronary blood flow per unit of work done is actually increased after administration of the drug.

Clinical studies reported recently have indicated that Ansiv produces considerable hypotension when administered either orally or intravenously to hypertensive subjects.[13] It is of great interest that in these subjects, renal vascular resistance fell during the early and late hypotensive phases but

rose during the "trough" of the response. Renal blood flow decreased as blood pressure reached its "trough" but was quite well maintained in the milder early and late hypotensive phases. Unfortunately, the clinical response has been transient and the side effects have been excessive when Ansiv was used as the sole agent in therapy.[13] Whether the drug, or its modifications, will eventually be useful is not known; however, its hemodynamic actions as reported[13] and as seen in the present study are of sufficient interest to merit consideration.

Conclusions

1. The systemic and coronary hemodynamic effects of 1-(2-methoxyphenol)-4-(3-methoxypropyl)-piperazine phosphate (Ansiv, HT 1479) have been studied by intravenous administration of the drug to a series of 10 anesthetized mongrel dogs.

2. Its administration was associated with a statistically significant decrease in peripheral and pulmonary arterial blood pressure and a decrease in right atrial pressure in 9 of the 10 animals.

3. Subsequent to its administration, cardiac output and coronary blood flow were maintained, whereas total peripheral resistance was reduced and coronary vascular resistance tended to be reduced.

4. After administration of the drug there was a considerable increase in cardiac rate and a slight but insignificant decrease in cardiac efficiency.

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A study of the normal Frank vectorcardiogram

*J. David Bristow, M.D.**
Portland, Ore.

The Frank system of spatial vectorcardiography has been proposed as an electrically orthogonal method and has an advantage in its ease of application. Its theoretical accuracy and the results of comparison with other corrected systems have provided a reasonable basis for its further investigation and clinical use. Despite this, there are few published guides for the differentiation of normal and abnormal vectorcardiograms obtained with this method. Some reports have presented experience with scalar leads recorded with the Frank system. Limited descriptions of the normal range are available, in terms of QRSsÊ and TsÊ loop axes.[1,2] These investigations included application of the system to patients with heart disease. Comparisons of the Frank system with the electrocardiogram[2,3] and other vectorcardiographic reference frames are available, but without detailed description of normal findings.[3-8] Spatial vectorcardiographic recording of the QRSsÊ loop with Frank leads was described by Seiden,[9] but information concerning the TsÊ loop and vector magnitudes was not given.

The purpose of this study was to obtain direct spatial vectorcardiograms (VCGs) with the Frank system in a group of subjects who were free of cardiovascular disease. The results are to serve as preliminary normal standards for use in comparison with findings in groups of subjects with pathologic conditions. It was of interest to compare the findings with those published for the SVEC-III and lead-field methods.

Material and Methods

Seventy-two subjects were studied. Fifty-three were faculty members, resident physicians, interns, or medical students at the University of Oregon Medical School Hospitals and Clinics. The remainder was constituted of inpatients in the University Hospitals. There were no findings or history of cardiac disease in any of the people included in the study. Routine 13-lead electrocardiograms, which were normal, were obtained just before or after the vectorcardiographic examination in all of the subjects. Because of the source of the subjects, only 4 women were included in the series. The age distribution of the group is shown in Table I.

The placement of electrodes and the lead resistance network employed were as proposed by Frank.[10] The fifth intercostal space at the sternal border was used in all cases as the level for the chest leads. Frank's point C, located 45 degrees between the anatomic axes of points A and E, was found by inspection. The examination was performed with the subject seated comfortably. The three planar projections of the VCG were photographed from the oscilloscope screen with a 35-millimeter camera. Exposures were made at the end of an ordinary expiration, with the breath held briefly. Sagittal projections were viewed from the left side, as previously recommended.[11] The film was projected in an enlarging viewbox with a screen 11 by 11 inches, and tracings were made on paper for definitive study. A 1-millivolt calibra-

Received for publication July 22, 1960.
*Raymond Brown Fellow in Cardiology, University of Oregon Medical School, Portland, Ore.

tion signal in the horizontal and vertical axes was also photographed to serve as a reference standard for the enlargements. The magnification provided traced records in which 3.5 inches (9.0 cm.) equalled 1 millivolt. Qualitative features of the loops were noted, and the tracings were divided into four quadrants through the isoelectric spot. Fig. 1 shows the reference frame which was used for the measurements. The maximum QRS and T vectors and the angle between them in each projection were measured. The angle and magnitude of terminal appendages were measured in the horizontal projection only. These resulted from late vectors in the right posterior quadrant. The terminal appendage was measured at the point at which the QRSsÊ loop turned abruptly to return to the isoelectric spot. Loops with a slight terminal curve to the right of the 90-270 degree axis were not considered to show a terminal appendage. Sharp angulation in the left posterior quadrant, followed by return to the isoelectric spot, also was not measured as a terminal appendage. The area of each quadrant of the QRSsÊ loop was determined by planimetry from the tracings of each projection and expressed as a percentage of the total QRS area for that projection. The QRSsÊ loop was then divided into equal half areas by a line through the isoelectric spot in each projection, as described by Pipberger.[12] This was done by planimetry by trial and error, and with practice could be done fairly rapidly. The angle of this axis is referred to as the half-area vector angle. It was considered to be the same as the maximum QRS vector in the frontal plane if the QRSsÊ loop was straight and very narrow, or linear. The angle between the half-area vector and the maximum vector of the TsÊ loop was measured in each projection. The PsÊ loops were quite small and were not studied in this project.

The recording equipment included a Tektronix Type 127 power supply with two 53/54E plug-in differential preamplifiers. The frequency response adjustments were set at 1 kilocycle for the high range and 0.06 cycle per second for the low. A Tektronix RM-32 oscilloscope was used for display of the loops. The beam was interrupted 1,000 times per second, and at lesser attenuations the direction of movement of the beam was indicated by the pointed leading edges of the time markings.

Table I. *Age distribution of the 72 subjects studied in this investigation*

Age	*Number of subjects*
19–29 yr.	28
30–39 yr.	25
40–49 yr.	10
50–59 yr.	2
60 yr. and over	7
Total	72

Results

The results of this study are presented in Table II. Whenever the data provided a Gaussian distribution, results are expressed as means and standard deviations. If a normal distribution was not found, ranges and means are given. The QRS-T and half-area T angles in the frontal projection were clearly one half of a normal distribution when plotted as population curves, with the majority of the values close to zero. Standard deviations were calculated for these by the formula $\sqrt{\frac{2\Sigma X^2}{2N-1}}$, assuming zero as the true mean.

Horizontal projection. The finding of most interest was the failure of the maximum QRS vector to provide a normal distribution when graphed as a distribution curve. There were two obvious groupings, with a small population with maximum vectors more posteriorly oriented than in the major group (Fig. 2). This was also noted with the SVEC-III system by Pipberger.[13] Calculations of the mean and standard deviation were performed for each of the two populations. These provide usable limits when two standard deviations from each mean are employed. When the frequency distribution of the half-area vector angles was plotted, a normal distribution was found, with narrower limits.

The absolute location of the TsÊ loop appeared to be a more dependable criterion than its measured relation to the maximum QRS vector. The maximum QRS vector–T angle data demonstrated two overlapping distributions, as would be anticipated from the spread of the maximum QRS vector

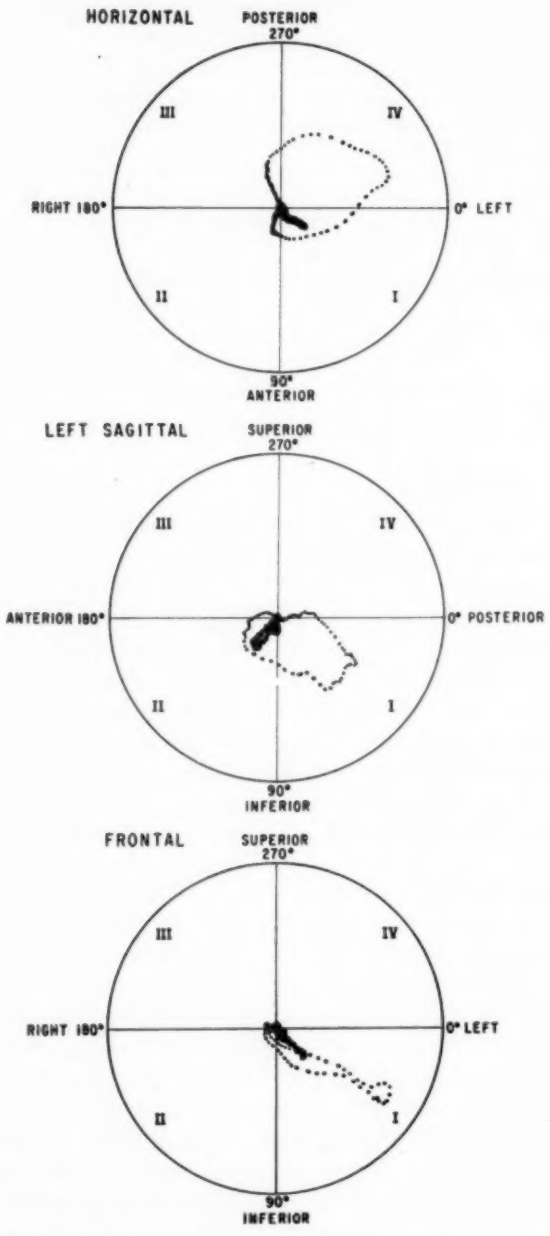

Fig. *1*. Reference frame used for angular measurements in this study. A representative VCG is shown for orientation. Time markings are 1,000 per second.

angles. The half-area vector T angle results were in a Gaussian curve, with a much narrower range. The TsÊ loop was anterior to the maximum QRS vector in all subjects except 2, and anterior to the half-area vector in all but one.

Initial anterior movement of the QRSsÊ loop, often slightly to the right, was observed in all subjects except one. This patient had an electrocardiogram which displayed normal R waves in the precordial leads, but had a VCG with initial posterior movement. This discrepancy is not explained, but Abildskov and associates[2] noted occasional deflections in the electrocardiogram which were not recorded with scalar Frank leads. The QRSsÊ loop was inscribed in a counterclockwise direction in all cases. Terminal appendages were present in 48 of the 72 subjects.

Sagittal projection. Once again there was a wide range of values for the angle of the maximum QRS vector and a peculiar frequency distribution with three peaks (Fig. 2). Means and standard deviations for the entire group and for each of the component populations provided similar 95 per cent limits (mean ± 2 standard deviations) if the outer two sets of limits from the three groups were compared to those for the whole. The calculation for the entire group as a single population is presented in Table II. The distribution curve for the half-area vector angles was Gaussian.

The QRSsÊ loop was initially anterior and superior or inferior in all cases except one. The direction of inscription was counterclockwise in 70, and 2 others had figure-of-eight configurations, with the early part of the loop counterclockwise.

Frontal projection. Much narrower ranges were found for the maximum QRS vector and T vector angles in this projection. The QRS-T angles were small. In general, there was no correlation between the angle of the maximum QRS vector and the direction of inscription of the QRSsÊ loop. However, counterclockwise inscription was not seen with loops whose maximum vector was beyond 45 degrees.

QRS areas. Wide ranges of values were found for the distribution of the percentage of QRS area in the various quadrants of each planar projection. However, certain narrow limits are considered worthy of mention. In the sagittal projection, only one QRSsÊ loop had over 5 per cent of the total sagittal QRS area initially superior to the isoelectric spot. The right anterior quadrant in the horizontal projection contained no more than 7 per cent of the total QRS area of that projection in any subject.

Discussion

In this study the angle of the maximum QRS vector did not appear to be a satisfactory diagnostic criterion in the hori-

zontal and sagittal projections. The ranges of normal values were large, and the maximum QRS vector–T angles had great variability. In the frontal projection, however, narrow normal distributions of values for these parameters were found. The angle of the half-area vector has been suggested by Pipberger[12] as a better measure than the maximum QRS vector angle, and, when used with the SVEC-III system, was found to be quite close to the angle of the mean QRS vector. When the half-area vector angles were measured in this study, a striking normality of distribution was found. This was in marked contrast to the data from the maximum QRS measurements in the horizontal and sagittal projections. These differences are exemplified by the VCGs shown in Fig. 3. Similarly, the half-area T vector angles fell into narrower ranges in these projections than the maximum QRS vector–T angles. It is suggested that the half-area vector angle has a useful place in the interpretation of the orthogonal vectorcardiogram. It is an easy measurement to perform and is much simpler than the calculation of the mean QRS axis from spatial loops or from area analysis of scalar leads.

It was hoped that measurement of the areas in various quadrants of the QRSsÊ loop in each projection would provide narrower ranges of values than those actually found. There were two places in which only a small part of the QRSsÊ loop was found normally. In the right anterior quadrant of the horizontal projection, no subject had over 7 per cent of the horizontal QRS area. This represented the earliest part of the loop. In the sagittal projection, all subjects, except one, had initial superiorly directed activity (in the anterior superior quadrant) of 5 per cent or less of the total sagittal QRS area. The single exception was 10 per cent. It is postulated that an increase in area beyond 5 per cent in this quadrant might correlate with the presence of small inferior myocardial infarctions, which have escaped detection by other electrocardiographic and vectorcardiographic means. Other criteria for the vectorcardiographic diagnosis of inferior infarction have been used. The angle of initial superiorly directed vectors in the sagittal projection was used by Milnor and associates[14] with the tetrahedron reference frame. Qualitative criteria have been employed.[15] It is our opinion that the measurement of an area resulting from both time and voltage may be a sensitive diagnostic aid in patients whose findings are otherwise equivocal. This will require clinicopathologic proof, of course. Certainly the "borderline" Q wave in Lead aV_F remains an unsolved problem, and one to which the orthogonal vectorcardiogram logically can be applied.

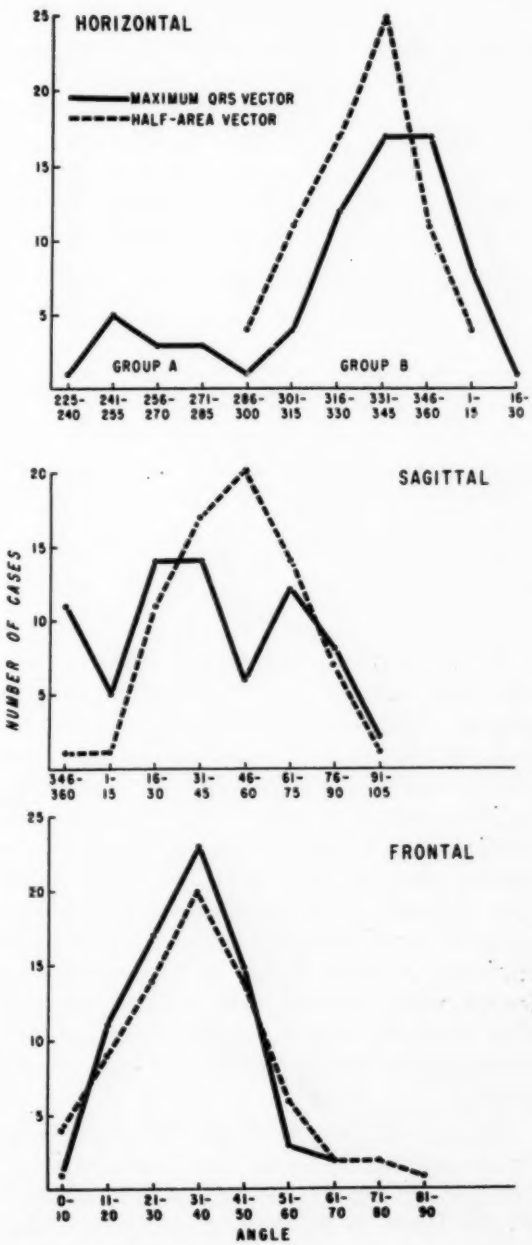

Fig. 2. Distributions of maximum QRS and half-area QRS vector angles in the three projections. See text for discussion.

Table II. *Results from analysis of VCGs in 72 subjects who were free of cardiac disease**

	Horizontal	*Left sagittal*	*Frontal*
Angle maximum QRS vector	Mean groups A and B: 327° Group A: 261 ± 17° Group B: 341 ± 17°	39 ± 30°	33 ± 13°
Angle half-area QRS vector	331 ± 18°	51 ± 20°	36 ± 17°
Magnitude maximum QRS vector	1.58 ± 0.37 mv.	1.24 ± 0.36 mv.	1.67 ± 0.45 mv.
Angle maximum T vector	37 ± 17°	135 ± 23°	37 ± 12°
Magnitude maximum T vector	0.51 ± 0.14 mv.	0.44 ± 0.12 mv.	0.47 ± 0.14 mv.
QRS–T angle	Range: 4°–166° Mean: 71°	96 ± 39°	Mean: 12° S.D.: 18° from zero†
Half-area vector—T angle	66 ± 27°	86 ± 30°	Mean: 15° S.D.: 20° from zero†
Angle terminal appendage	Range: 228–268° Mean: 253°		
Magnitude terminal appendage	Range: 0.35–1.89 mv. Mean: 0.94 mv.		
Direction of inscription	Counterclockwise: 72	Clockwise: 70 Figure-of-8: 2	Clockwise: 40 Counterclockwise: 9 Figure-of-8: 23

*When normal distributions of data were found, values given are means and standard deviations. Otherwise, means and ranges are listed. Standard deviations were calculated for the QRS-T and half-area vector T angles in the frontal projection by the formula $\sqrt{\frac{2\Sigma X^2}{2N-1}}$, since these parameters provided one half of a normal distribution.

†See text.

Our results were compared with the available experience of others who have used this system. Abildskov and associates,[2] in describing studies with scalar recording of the Frank leads, concentrated their attention on its comparison with the clinical electrocardiogram. However, calculation of the frontal plane QRS axis from the algebraic sum of positive and negative deflections in leads X and Y was performed for 91 normal subjects. A mean value of 33 degrees was found, with a range from 0 to 67 degrees. The mean for the maximum frontal plane QRS vector in our group was also 33 degrees.

As part of a study of the VCG in arterial hypertension, Libretti and Zanchetti[1] reported the results of scalar recording of Frank leads in 26 normal subjects. Mean QRS vectors were calculated from area analysis of the scalar tracings. If the means for the planar half-area vector angles in the present series are compared with their results, reasonably similar values are found. The exception is in the sagittal projection, in which the values from the two studies are 16 degrees apart. Means and the means ± 2 standard deviations are shown in Table III. The similarity of values from these two investigations lends support indirectly to the hypothesis that the planar half-area vector is close to the planar mean QRS vector in this lead system, at least in normal people.

Investigators have studied the differences between various vectorcardiographic methods, including the Frank method. However, little information was found concerning spatial display of Frank leads in normal subjects during a search through the literature.

One of the limiting factors in the clinical application of spatial vectorcardiography has been the well-recognized poor corre-

spondence between VCGs obtained with different lead systems. If recently developed systems are electrically orthogonal, as proposed, and if the basic tenets of vectorcardiography are true, reasonably interchangeable data should be obtained with different corrected systems. The Frank system was described as giving good correspondence with the SVEC-III system in a study in which leads from four orthogonal methods were interchanged.[7] After comparing the Frank, SVEC-III, lead-field, and Helm systems, the authors concluded that the four systems were interchangeable by current clinical standards in normal subjects and in the majority of abnormal subjects. This view was not completely acceptable to Simonson and associates,[16] who performed a comparative study of eight vectorcardiographic systems. Their analysis apparently did not include the Frank system as herein used. Pipberger[4] concluded that the SVEC-III and Frank methods were close in lead strength, and that angular discrepancies between the two were of minor degree only.

It was therefore of considerable interest to us to compare our results with those available from a study of the SVEC-III in normal subjects.[13] In the horizontal projection, the mean for the angle of the maximum QRS vector is 4 degrees different in the two studies. The distribution curves for this parameter are similar, with separate peaks in the 330 to 15 degree segment and to the right of the 270 degree line. The results from the frontal projection suggest that the QRSsÊ loop as seen with the Frank system is located slightly higher than with the SVEC-III (Table IV). The results for the T vector are close, with the greatest difference between means (7 degrees) present

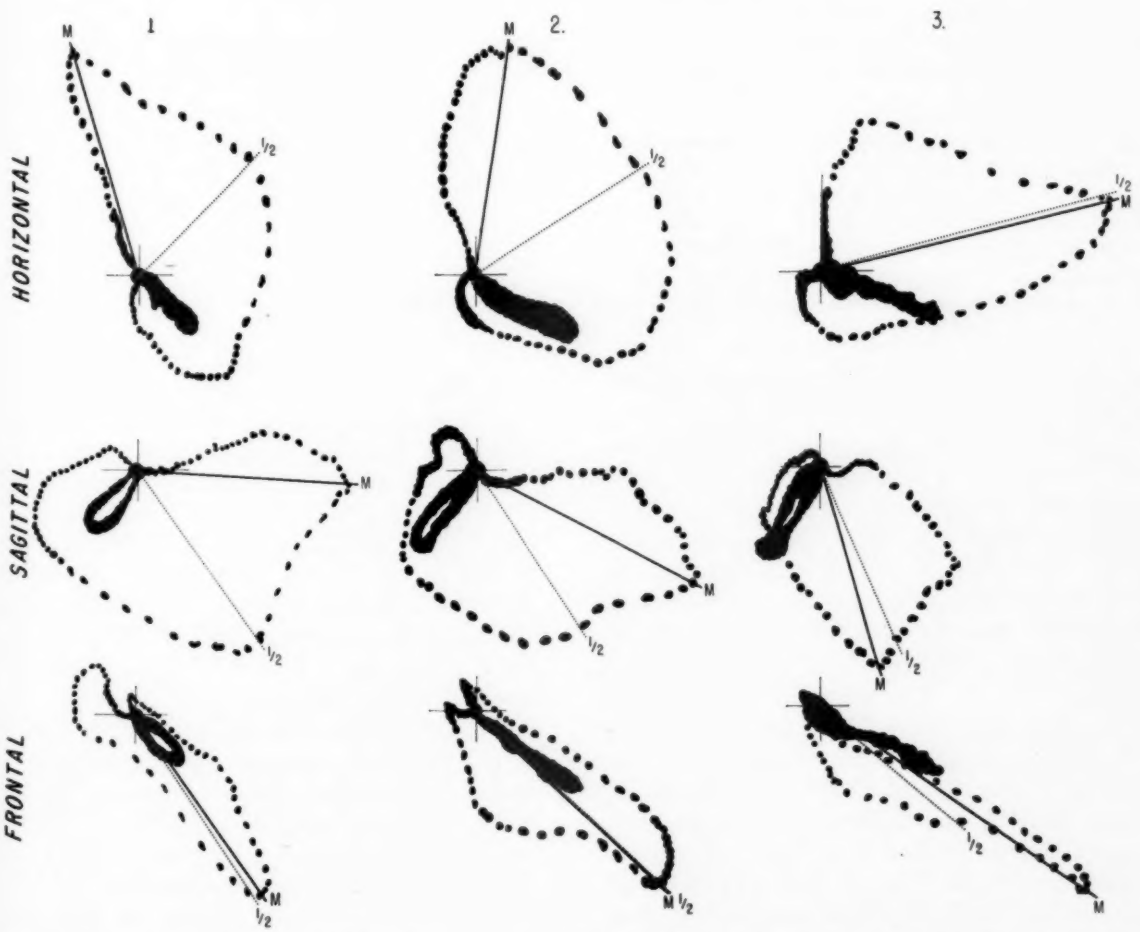

Fig. 3. Traced records from VCGs of 3 normal subjects. Widely different maximum QRS vector angles are present in the horizontal and sagittal projections. Less variation is seen when half-area QRS vector angles are compared. Time markings are 1,000 per second.

Table III. *Comparison of two studies with the Frank system in subjects without heart disease**

	QRS angle			*T angle*		
	H	*S*	*F*	*H*	*S*	*F*
Libretti and Zanchetti: QRS and T area vector angles	290–22 (336)	13–121 (67)	10–70 (40)	3–71 (37)	93–169 (131)	9–73 (41)
This series: Half-area QRS and maximum T vector angles	295–7 (331)	11–91 (51)	2–70 (36)	3–71 (37)	89–181 (135)	13–61 (37)

*Values from the investigation by Zanchetti and Libretti[1] were converted to the reference frame employed in the study herein reported. Means are indicated in parentheses, and the ranges listed are means ± 2 standard deviations. See text for discussion.

Table IV. *Comparison of values from three orthogonal vectorcardiographic methods**

	QRS angle			*T angle*		
	H	*S*	*F*	*H*	*S*	*F*
Frank system (this series): Maximum QRS and T vector angles	227–15 (327) 2 populations (see text)	339–99 (39)	7–59 (33)	5–71 (37)	89–181 (135)	13–61 (37)
SVEC–III (Pipberger[13]): Maximum QRS and T vector angles	242–44 (323) Not Gaussian	342–128 (55)	11–71 (41)	355–81 (38)	90–172 (131)	20–68 (44)
Lead-field (Jordan and Beswick[17]): Main QRS loop axis and maximum T vector angles (39 selected patients)	269–333 (301)	25–81 (53)	38–86 (62)	32–92 (62)	101–173 (137)	42–78 (60)

*Values from the SVEC-III and lead-field studies were converted to the reference frame used in the Frank series. Means are in parentheses, and the ranges listed are means ± 2 standard deviations. See text for discussion.

in the frontal projection. When recommended corrections were made for the originally published amplitude data for the SVEC-III, it was found that the maximum QRS vectors were 10 to 20 per cent larger in this study. Scalar component leads were not recorded in this investigation, so that accurate timing of various events in the loops was not possible for comparison with those presented by Pipberger in his analysis of the normal SVEC-III results.

Jordan and Beswick[17] applied a vectorcardiographic system developed from the lead-field concept of McFee and Johnston to 47 healthy young men. The results were described for 39 and 8 of these subjects as separate groups. The 39 had VCGs which were all quite similar. The smaller group of 8 had more widely varying loop parameters. These workers employed the "main loop axis" as one measurement of the QRSsÊ loop. This axis was the vector in the middle of the loop in time, and apparently was very close to the maximum QRS vector. A comparison of these values for their larger group and the maximum QRS vectors from this series, as well as T vectors, can be seen in Table IV. From these data and their published photographs, it appears that the lead-field system employed by Jordan and Beswick produces QRSsÊ loops which are more often posteriorly and inferiorly oriented than those obtained with the Frank and SVEC-III systems. The means ± 2 standard deviations provide much narrower limits for their main loop QRS axis and T vector angles than the maximum QRS and T vector angles which we obtained with the Frank leads. However, when the half-area vector angles from our study are compared with the mean manifest QRS axes from the lead-field system, 95 per cent limits of ap-

proximately equal spread are found, although with the same difference in location previously described.

In a review of the literature, no data were found from study of normal subjects with the corrected system designed by Helm.[18]

It is obvious that any careful quantitative comparison of different lead systems requires their application to a single group of subjects. However, in comparing the groups previously described, the differences in results with the lead-field method appear to be outside the expected range of variability on the basis of testing different subject populations. Whether or not there will be more variable findings with the lead-field method in older subjects will require investigation.

Summary

An investigation was performed with spatial vectorcardiographic recording of Frank leads in a group of 72 subjects who were free of cardiovascular disease. Study of the vectorcardiograms included measurement of the angle of the half-area vectors in each planar projection of the QRSsÊ loop. This parameter provided a narrower range of distribution in the horizontal and sagittal projections than the angle of the maximum QRS vector. Information concerning QRS and T vector magnitudes is presented.

The results of this study are compared with the limited information available from application of this lead system to normal subjects, and with published data for the SVEC-III and lead-field methods.

The author wishes to express appreciation to Dr. H. E. Griswold for his encouragement and support of this project.

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Angina pectoris
Effect of exertion and of nitrites on precordial movements

*N. Sheldon Skinner, Jr., M.D.**
Robert S. Leibeskind, M.D.
Harry L. Phillips, M.D.
T. R. Harrison, M.D.
Birmingham, Ala.

Previous studies from this laboratory[1,2] have shown that the majority of patients with angina pectoris develop a midsystolic outward movement (bulge) of the precordium at the time of pain, and that this abnormal deflection either diminishes or disappears when pain is relieved by the administration of glyceryl trinitrate. The present communication offers further evidence along these lines, and is also concerned with additional aspects of precordial motion in such patients. Some support for the concept that subthreshold exertion is beneficial in patients with coronary insufficiency will be offered, as well as evidence for the presence of temporary heart failure at the time of anginal pain. The effects of three coronary dilator drugs, glyceryl trinitrate tablets (GTN), glyceryl trinitrate ointment (GTNO), and pentaerythritol trinitrate (PETN), on recorded precordial movements from patients with deficient myocardial oxygenation will be presented.

Methods

Low-frequency precordial motions (kinetocardiograms; KCG) were recorded in 11 patients with typical angina pectoris. Tracings were made at the end of a normal expiration by the bellows-crossbar technique,[3] by means of a six-channel Sanborn direct writer. Electrocardiographic and carotid pulse curves were secured simultaneously. Each patient then exercised while recumbent, by moving a 10-pound pulley-weight system a distance of 8 feet every 3 seconds. A critical level of exertion, i.e., a level which would produce pain, electrocardiographic evidence of ischemia, or the kinetocardiographic changes previously described[1,2] as characteristic of anginal attacks, was then determined for each subject. This was done by using an initial exercise period of 20 seconds and then 20-second increments until one or all of the above-mentioned criteria were met. Such a level was termed the "threshold exercise" for the particular patient.

After these preliminary observations the effect of a long-acting nitrite was investigated; the patient received either GTNO the first day and PETN the second, or was given these substances in the reverse sequence. The doses employed were either 1½ inches of 2 per cent GTNO spread

From the Department of Medicine, Medical College of Alabama, Birmingham, Ala.
Aided by grants from the Calhoun County Heart Association, and the Robert Wood Johnson Foundation, and by a gift from the late Frank L. Miller, Jr.
Received for publication Aug. 12, 1960.
*Predoctoral Fellow of the United States Public Health Service.

thinly on the skin or 20 mg. of PETN orally. Resting and "threshold exertional" records were secured at ½ hour and at intervals of 1, 2, 3, and 4 hours after the drugs.

The tracings in a given individual were made from identical precordial points which had been selected during the preliminary observations as those areas which exhibited the most striking abnormalities during anginal attacks. In most instances these were the fourth or fifth left intercostal spaces in the V_3 or V_4 lines.

Three different precordial motions were often found to be grossly abnormal during anginal attacks and were, therefore, analyzed in detail. These motions were: (1) the forward movement (atrial upstroke; AU), starting shortly after the onset of the P wave of the ECG; (2) the large inward deflection (ejection downstroke; ED), beginning about the time of the carotid pulse; and (3) a large mid-systolic outward motion (bulge; B). This last motion apparently corresponds to the systolic ballooning of localized ischemic areas in the dog heart, as described by Tennant and Wiggers[4] and by Prinzmetal and associates.[5] The magnitudes of these three movements were measured in all traces and expressed as percentage of the total amplitude (TA) of the cardiac cycle. The method of measurement is indicated in Fig. 1. It should be noted that impaired ventricular contraction is indicated by a *decrease* in the ratio Ejection Downstroke/Total Amplitude or by an *increase* either in Atrial Upstroke/Total Amplitude or Bulge/Total Amplitude.

When the findings with the two long-acting drugs were compared, it was necessary to allow for spontaneous variations in the records. Although these variations are very slight in healthy persons, they may be large in patients with angina. Alterations, after therapy, in the size of a given motion which were less than 10 per cent of the total amplitude of the record were, therefore, arbitrarily considered to be without significance. An additional correction was introduced by subtracting from the number of "beneficial changes" the number of "harmful changes" which were encountered after the same drug. A change toward the typical record of healthy young adults is considered as "beneficial"; the opposite is deemed to be "harmful." Since there is no evidence that either PETN or GTNO depresses myocardial contraction, it was assumed that these apparently harmful alterations were actually due to pure chance, and that an equal number of apparently beneficial alterations might also have occurred had the drug never been administered. Although these procedures probably tend to minimize the value of each

Table I. *Effect of subthreshold* and threshold† exertion on the parameters studied*

Name	*Resting control* (%)	*Subthreshold exercise* (%)	*Threshold exercise* (%)
Atrial Upstroke–Total Amplitude Ratio			
1. M. W.	50	21	47
2. E. B.	38	26	65
3. C. F.	51	8	4
4. H. A.	29	22	47
5. H. W.	43	56	63
6. C. H.	4	10	2
7. A. S.	10	4	5
8. M. D.	—	—	—
9. J. M.	23	3	3
10. R. C.	11	7	11
11. J. J.	8	6	10
Ejection Downstroke–Total Amplitude Ratio			
1. M. W.	50	58	20
2. E. B.	53	70	2
3. C. F.	12	11	13
4. H. A.	65	63	47
5. H. W.	14	34	31
6. C. H.	25	75	4
7. A. S.	55	68	58
8. M. D.	3	13	7
9. J. M.	72	74	20
10. R. C.	27	16	28
11. J. J.	51	38	49
Bulge–Total Amplitude Ratio			
1. M. W.	77	37	60
2. E. B.	0	0	62
3. C. F.	13	8	16
4. H. A.	45	37	25
5. H. W.	8	6	16
6. C. H.	6	5	63
7. A. S.	37	28	26
8. M. D.	49	42	68
9. J. M.	3	0	4
10. R. C.	12	13	15
11. J. J.	33	10	58

*Exercise level less than that required to produce evidence of angina pectoris.
†Exercise level sufficient to produce evidence of angina pectoris.

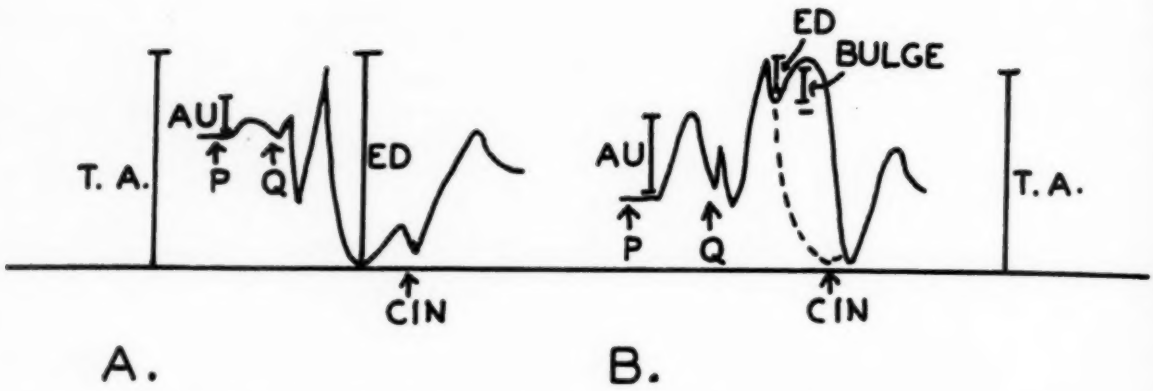

Fig. *1.* Comparison of the normal and abnormal relationships of the specific movements studied. *A* and *B* are diagrams of typical records obtained from the apical region (K_{45} or V_4 position of the ECG). *A*, Normal person. Note the small atrial upstroke and large ventricular ejection downstroke motions. Total amplitude is shown extending from the highest to the lowest recorded point of the entire complex. *B*, Angina at time of pain. The abnormally large atrial upstroke, the markedly decreased ventricular ejection downstroke, and the mid-systolic outward movement (bulge) are shown. Any one or all of these may appear during anginal pain. *T.A.:* Total amplitude of the entire complex. *AU:* Atrial upstroke movement. *ED:* Ventricular ejection downstroke movement. *CIN:* Carotid incisural notch. *P:* P wave of the ECG. *Q:* Q wave of the ECG.

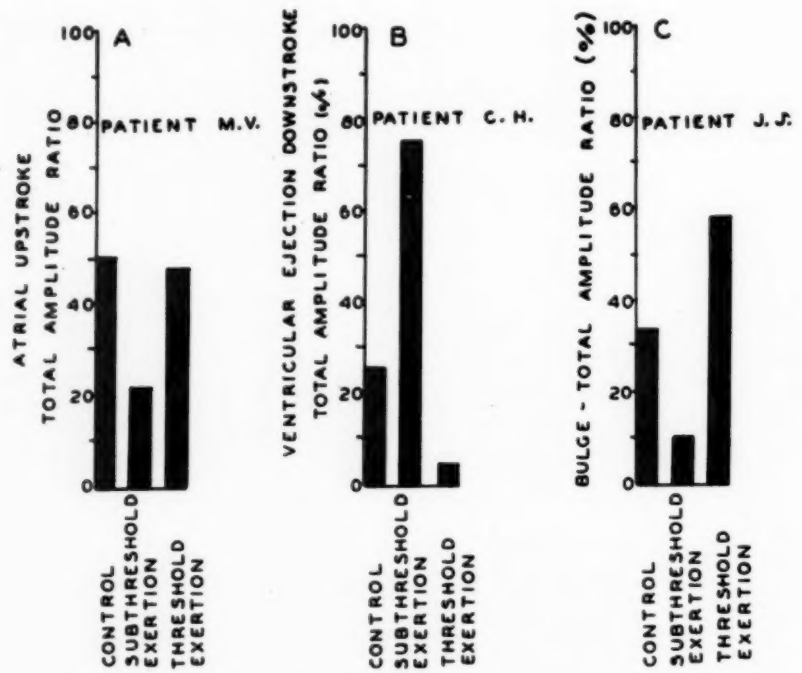

Fig. *2.* This figure shows the effect of subthreshold (exercise level *insufficient* to produce evidence of angina pectoris) and threshold (exercise level *sufficient* to produce objective or symptomatic evidence of angina pectoris) exertion on the three parameters studied. *A*, Patient M. W. with an abnormal AU/TA at rest showed a marked decrease (to within normal limits) after subthreshold exertion. With greater (threshold) exertion this value approached those obtained for control. *B*, Patient C. A. had an increase in ED/TA of three times resting value after a level of exertion insufficient to produce evidence of angina pectoris; however, with an increased amount of effort, which produced severe anginal pain, this movement almost completely disappeared. *C*, Patient J. J. with a moderate bulge at rest but without pain showed a pronounced decrease in this motion after minimal exertion. After greater effort a marked increase in this mid-systolic outward movement occurred. Thus, this figure demonstrates that degrees of effort that are insufficient to produce objective or symptomatic evidence of angina pectoris apparently have beneficial effects on precordial movements.

drug, it would seem that they increase the validity of the comparison between them.

Results

Effect of graduated increments of exercise. The normal amplitude of the atrial upstroke in relation to the total excursion is usually less than 25 per cent and always less than 33 per cent.[6,7] Four of 5 patients who showed high ratios at *rest* had lower values after *subthreshold* exertion. With further physical effort (to the point of anginal pain or ECG evidence of ischemia) the ratios tended to rise again to abnormal levels (Table I; Fig. 2).

After less exertion than that required to produce pain, 6 patients displayed an increase, as compared to resting values, in the ventricular ejection downstroke–total amplitude ratio (ED/TA); 2 showed a decrease, and 3 showed essentially no change. With threshold exertion, 5 had less than resting percentages, 5 were unchanged, and 1 had an increase. Thus, in approximately half of the subjects, mild exertion caused improvement, and additional effort caused impairment of the inward movement of ejection (Table I; Fig. 2).

Six of the 7 patients with a definite recordable bulge (B) while at rest showed a decrease in this movement after subthreshold exertion; 1 was unchanged. With greater exercise, 5 increased in their bulge–total amplitude ratio, 1 decreased, and 1 remained the same. The other 4 patients had no definite bulge with the lesser level

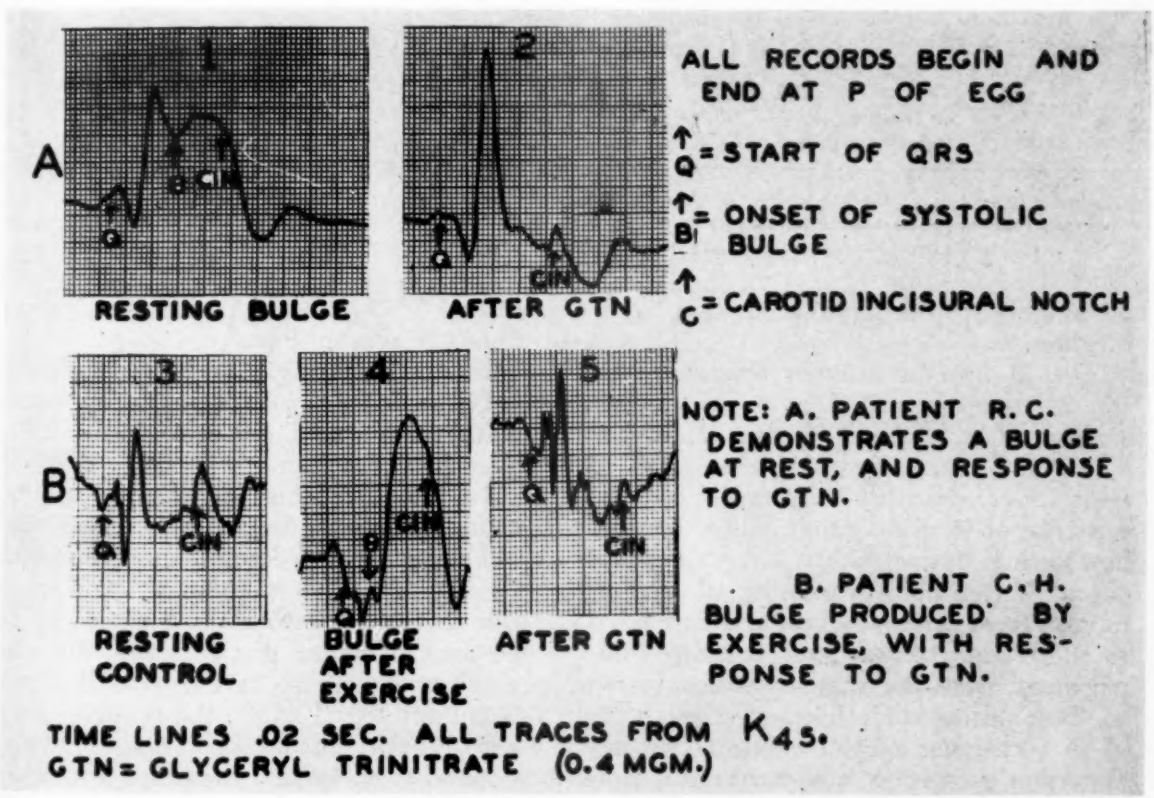

Fig. *3*. Paper speed, 50 mm. per second. Tracings taken from K_{45} regions in each of two patients with angina pectoris. *A*, Records obtained from Patient R. C. at a time when no pain and no ECG change of acute ischemia were present. *1*, The record at rest shows the markedly reduced ventricular ejection downstroke movement and the prominent mid-systolic outward movement (bulge) (see text). *2*, Two minutes after one sublingual tablet of glyceryl trinitrate (0.4 mg.), with no detectable change in blood pressure. Note the increase in the ventricular ejection downstroke and the absence of the previous mid-systolic outward movement. *B*, Records obtained from Patient C. H. at rest, after exercise, and after glyceryl trinitrate. *3*, The record at rest shows no mid-systolic outward movement and a prominent ventricular ejection downstroke movement. *4*, After 1½ minutes of mild exercise sufficient to produce pain and ECG changes compatible with acute myocardial ischemia. Note the almost absent ventricular ejection downstroke movement and the large mid-systolic outward movement. *5*, Two minutes after one sublingual tablet of glyceryl trinitrate (0.4 mg.), with no detectable change in blood pressure. Note the similarity of this record with record *3*.

Table II. *Alterations* in precordial motions after long-acting nitrites†*

Time after drug	Number of observations	Effects	Decrease in AU/TA ratio				Decrease in B/TA ratio				Increase in ED/TA ratio			
			After GTNO		After PETN		After GTNO		After PETN		After GTNO		After PETN	
			Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
½ hr.	10	Positive	4	3	1	2	4	6	3	1	4	6	1	2
		No change	5	5	8	7	6	4	6	6	6	1	8	5
		Opposite	0	1	0	0	0	0	0	1	0	2	1	1
1 hr.	11	Positive	4	3	0	2	4	7	5	4	4	8	1	4
		No change	6	6	10	7	4	3	5	4	6	1	8	4
		Opposite	0	1	0	1	1	0	0	1	0	1	1	1
2 hr.	11	Positive	4	2	0	2	4	7	3	3	2	6	2	3
		No change	4	8	9	8	6	3	6	6	6	3	5	6
		Opposite	2	0	1	0	0	0	1	0	2	1	3	0
3 hr.	11	Positive	3	3	0	3	3	5	5	1	1	4	3	3
		No change	5	7	7	6	7	5	5	8	7	5	7	6
		Opposite	2	0	3	1	0	0	0	0	2	1	0	0
4 hr.	11	Positive	3	2	0	3	5	5	5	3	6	7	2	3
		No change	6	6	8	5	5	3	5	7	1	2	7	5
		Opposite	1	2	2	2	0	2	0	0	3	1	1	1

*Changes of 10 per cent or less of the total amplitude are listed as "no change."

†The exercise utilized was "threshold," i.e., that which in the absence of the drug produced clinical (pain), electrocardiographic (sagging S-T), or kinetocardiographic (increased atrial upstroke, bulge, or decreased ejection downstroke) evidence of ischemia.

of effort but did have after the larger exertion.

After a level of exertion less than that required to produce objective or symptomatic evidence of ischemia, 10 of the 11 subjects displayed one or more objective signs of improved contractility (*decrease* in atrial upstroke or in mid-systolic bulge, *increase* in ejection downstroke). After threshold effort, 9 exhibited worsening of one or more of these three movements as compared to the resting record, and all showed impairment when the values were compared to those during the milder exercise.

An occasional subject exhibited grossly abnormal precordial movements at a time when pain was absent and the ECG was normal.

The similarity of the precordial movements during anginal attacks to those in patients with congestive heart failure will be considered later.

The effects of nitrites. The data are presented in detail in Tables II and III and are illustrated in Figs. 3, 4, and 5.

When the immediately preceding record was abnormal, sublingual glyceryl trinitrate (GTN, nitroglycerin) usually produced a prompt change toward or to a normal configuration (Fig. 3; Table III).

Both GTNO (nitroglycerin ointment) and PETN (pentaerythritol tetranitrate) also had pronounced effects. These involved not only the prevention of pain but also the lessening or disappearance of such abnormalities as were present in the resting records, and the prevention of the deterioration caused by threshold exercise in the absence of these drugs. Thus, the postexertional increase in the atrial upstroke was inhibited (Fig. 4), the relative size of the ejection downstroke was usually increased (Fig. 5), and the bulge was diminished or abolished. When these abnormalities were present during the control studies, they became less pronounced in each subject at some time during the 4-hour period after the two drugs.

The previous clinical impression that GTNO is usually more efficacious[8] was sustained. This is clearly shown in Tables II and III. Because of the rigid criteria used for considering a result as beneficial, these tables tend to minimize the value

of both drugs. Certainly, the effect of GTNO in preventing anginal pain has been more consistent than would appear from the tables. In the doses employed in this study the ointment was not always superior; the reverse effect was sometimes encountered (Figs. 4 and 5).

The onset, peak, and duration of effect of the drugs varied in the different subjects, but, in general, appeared, respectively, to be at about ½ hour, 1 hour, and 4 to 6 hours after their administration.

Discussion

The beneficial effects caused by nitrites are presumably to be ascribed to a favorable influence on the Coronary Flow/Heart Work ratio. Recent reports[9,10] would suggest that decrease in work rather than increase in perfusion may be responsible. However, our studies, although supplying no conclusive data on this question, make it appear likely that the improvement was related to augmentation of coronary blood flow. No consistent or significant decline in blood pressure was observed at the time of drug-induced improvement. Cardiac output was not measured during these experiments but the data of others[11] indicate no decrease after glyceryl trinitrate. It seems improbable, therefore, that a striking decline in peripheral resistance or cardiac work occurred. Furthermore, the changes induced by subthreshold exercise, which were directionally similar to those caused by nitrites, cannot readily be explained in terms of decrease in the work of the heart.

This tentative conclusion, that the beneficial effects of nitrites are due to increase in coronary flow, is at variance with the more direct data as obtained by the nitrous oxide method. However, the validity of this procedure in patients with coronary disease remains to be established. In view of the proved existence of undisputed arterial collaterals,[12] the venous drainage may also occur through pathways which are different from those in the normal person. If so, the basic assumption of the nitrous oxide

Table III. *Summary of effects of nitrites on precordial movements**

Time after administration	*Effect on precordial motions*	*Glyceryl trinitrate† (sublingual)*		*Glyceryl trinitrate ointment‡*		*Pentaerythritol tetranitrate‡*	
		Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
3-5 min.	Observations	18	18				
	Beneficial	15	17				
	Harmful	1	0				
30 min.	Observations			29	28	28	25
	Beneficial			12	15	5	5
	Harmful			0	3	1	2
1 hr.	Observations			29	30	30	28
	Beneficial			12	18	6	10
	Harmful			1	2	4	3
2 hr.	Observations			30	30	30	28
	Beneficial			10	15	5	8
	Harmful			4	1	5	0
3 hr.	Observations			30	30	30	28
	Beneficial			7	12	8	7
	Harmful			4	1	3	1
4 hr.	Observations			30	30	30	29
	Beneficial			14	14	7	9
	Harmful			4	5	3	3
Totals for all observations	Observations			296		286	
	Beneficial			129		70	
	Harmful			25		24	
Excess of beneficial over harmful effects				104		46	

*Effects recorded as beneficial or harmful according to whether record became more or less like those of healthy young persons. Alterations of less than 10 per cent of total amplitude were considered to be no change.
†As tested on subjects with abnormal records. Little effect if preceding record was normal.
‡All tests reported whether motions before drug were or were not abnormal.

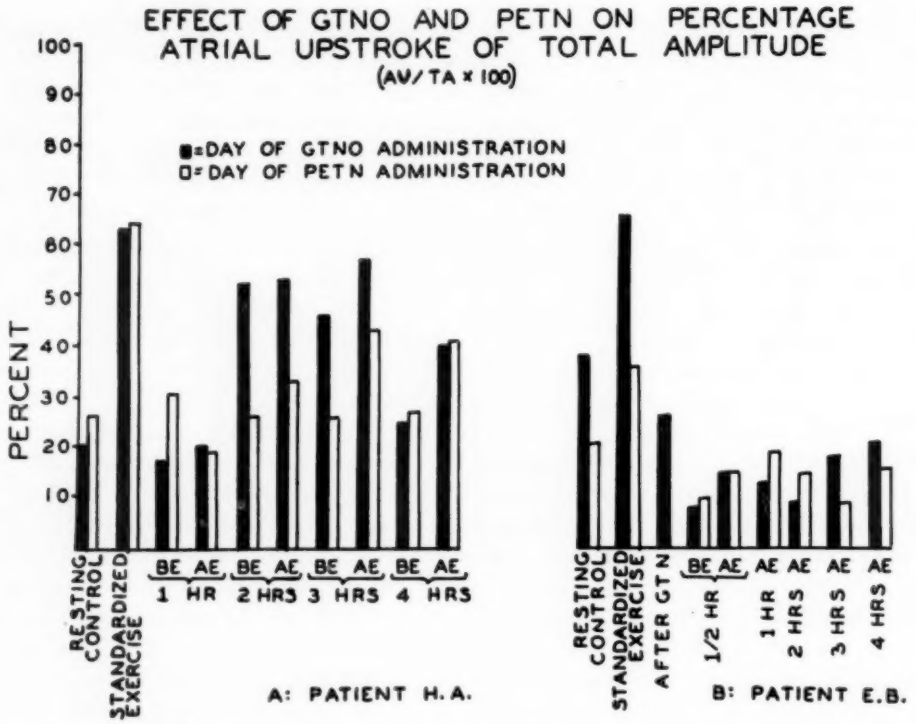

Fig. 4. Comparison of the effect of two long-acting coronary dilator drugs (GTNO and PETN) on the atrial upstroke–total amplitude ratio (see also Fig. 1) in 2 patients with angina pectoris. Resting control and standardized exercise records were made prior to the administration of each drug, and the effect of each compared was studied at hourly intervals for 4 hours before and after the described exercise (see text). *A*, The percentage AU of TA remained below the "standardized exercise level," before and after exertion after the administration of both drugs but not below the resting control level. PETN (20 mg. in a single oral dose) produced a slightly better response. *Note the large increase in percentage AU of TA produced by effort when the patient was not protected by coronary dilator drugs. B*, The percentage atrial upstroke of total amplitude in Patient E. B. decreased below resting control and "standardized exercise levels" after the administration of each drug. An approximately equal response to PETN and GTNO was noted. *Again, note the large percentage atrial upstroke produced by exercise when the patient was not protected with the coronary dilator drugs.* GTNO: Glyceryl trinitrate ointment (1½ inches). PETN: Pentaerythritol tetranitrate (20 mg.). GTN: Glyceryl trinitrate (0.4 mg. sublingually). *BE:* Before standardized exercise. *AB:* After standardized exercise.

method that the coronary sinus drains the left ventricle becomes unsound.

The observation that subthreshold exercise produces improvement in precordial motions, although seemingly paradoxical, is in accord with William Heberden's observations as stated in his original report.[13] We interpret it to mean that, in patients with angina, the coronary blood flow is initially more increased by slight exertion than is the myocardial oxygen need.[2] With greater (i.e., threshold) effort the reverse apparently occurs.

An alternative explanation for some of the beneficial effects of slight exercise in certain patients is as follows: The combination of diminished peripheral resistance[14] and augmented contractility[15] may produce increased systolic emptying, with decline in ventricular end-diastolic and atrial pressures. This would cause diminished stretch and decreased contraction of the atria. This sequence would account for the observed decrease in those precordial motions which are of atrial origin. However, it is difficult to explain the effect of mild exercise in causing disappearance of the systolic bulge and in producing the increased ejection downstroke, unless one assumes either: (a) that the coronary flow is increased, or (b) that the myocardial oxygen consumption is diminished, or (c) that there is simultaneous marked increase in myocardial efficiency associated with

decline in the coronary venous saturation. The two latter assumptions would appear to be improbable.

Müller and Rφrvik[11] have observed abrupt increase in pulmonary capillary (wedge) pressure during anginal attacks. This clear evidence of temporary left ventricular failure is supported by the present observations. The changes which we have found in precordial motions (increased atrial upstroke, large mid-systolic outward deflection, diminished inward movement of ejection) during anginal episodes are similar to those observed in patients with advanced congestive failure.[16] These abnormalities either diminish or disappear entirely when compensation is restored. An investigation of the effects of digitalis on precordial motions during anginal attacks is in progress and will be reported at a later date.

These observations are confirmatory of previous studies from this laboratory[1,2] in showing that myocardial ischemia of sufficient severity to impair the contractile function may exist in the absence of pain or electrical abnormality. The comparative value of the history, the exertional electrocardiogram, the ballistocardiogram, and the precordial movements in the diagnosis of atypical angina can only be settled by the study of a much larger group of patients.

Summary

1. In some patients with angina pectoris the precordial motions were normal at rest; in others, they were grossly deranged, even when pain was absent and the electrocardiogram was normal.

2. The three common abnormalities were an increase in atrial motion, mid-systolic outward bulge, and diminished inward motion during rapid ejection.

3. In 10 of 11 instances, one or more of these derangements improved after exertion (subthreshold) which was considerably

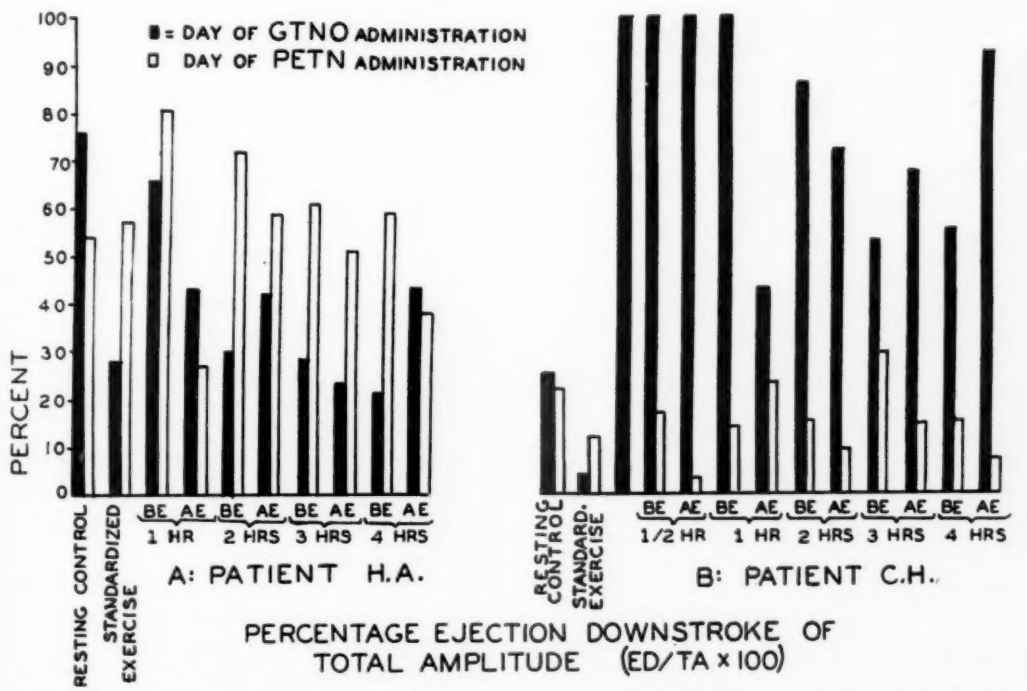

Fig. 5. The effect of exercise when sufficient to produce anginal pain on the ventricular ejection downstroke–total amplitude ratio. The effects of two long-acting coronary dilator drugs, GTNO and PETN, are shown. *A*, Patient H. A. displayed only a minimal to moderate response to GTNO, but a marked, sustained response to PETN, the latter persisting for the entire 4-hour study. *B*, Patient C. H. received minimal protective benefit from PETN but did have a marked effect from GTNO. Note that the relative ejection downstroke percentage increased two to five times after an exercise level which, prior to the administration of a coronary dilator drug, was sufficient to produce severe anginal pain. This figure shows the individual variation in response to various coronary dilator drugs. GTN: Glyceryl trinitrate (0.4 mg. sublingually). GTNO: Glyceryl trinitrate ointment (1½ inches). PETN: Pentaerythritol tetranitrate (20 mg.). *BE*: Before standardized exercise. *AE*: After standardized exercise.

less than that required to produce pain or other evidence of myocardial ischemia.

4. More strenuous (threshold) exertion caused exaggeration of one or more of these abnormalities when they had been previously present, and induced their appearance when previously absent.

5. Sublingual glyceryl trinitrate caused these distortions to decrease markedly or to disappear in 32 of 36 trials.

6. Glyceryl trinitrate ointment and pentaerythritol tetranitrate tablets both exerted a beneficial effect in tending to diminish or abolish abnormal motions. Although the ointment was usually the more effective drug, the oral preparation appeared to be better in some instances.

7. Data concerning the onset, peak, and duration of action of these two drugs are presented.

8. The findings offer indirect evidence for the "increased coronary flow" in contrast to the "diminished cardiac work" hypothesis as to the mechanism responsible for the improvement produced by nitrites.

9. In so far as can be judged from precordial motions, the temporary changes in myocardial contraction during anginal attacks are similar to those which occur during congestive heart failure and disappear as improvement occurs.

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Case reports

An unusual type of intermittent A-V dissociation in acute rheumatic myocarditis

Richard M. Goodman, M.D.
Alfred Pick, M.D.
Chicago, Ill.

Involvement of the A-V node has been well documented in cases of active rheumatic myocarditis. The inflammatory and vascular changes that are produced in this region may give rise to a variety of arrhythmias,[1] and among these, A-V dissociation is one of the most interesting. The case to be presented illustrates some problems of interpretation that may arise when, in acute rheumatic fever, A-V junctional tissues are involved by the pathologic process and become the site of an additional ectopic pacemaker. Detailed analysis of the electrocardiograms provided an opportunity (a) to study mechanisms of intermittence of A-V dissociation and of temporary synchronization ("accrochage")[2] of atrial and ventricular action, and (b) to reappraise the role of ventricular fusion beats in the distinction between ectopic rhythms of supraventricular origin and those of ventricular origin.[3]

Case report

J. H., a 15-year-old Negro boy, entered the Cook County Hospital on April 23, 1960, complaining of pain and swelling of the right ankle and precordial pain which had been present for the previous 4 days. The patient stated that he was perfectly well until 1 month prior to admission, at which time he had a sore throat. He did not receive any medication for his pharyngitis at that time. Ten days prior to admission he developed headache and fever; 3 days later he noticed pain and swelling (migratory in nature) of the left knee, left ankle, and both elbows. Two days prior to admission he had a recurrence of sore throat and developed precordial chest pain.

Physical examination. The patient was a well-nourished, well-developed young Negro boy in no acute distress. His temperature was 101°F. orally, the pulse varied from 70 to 80 per minute, respirations were 16 per minute, and blood pressure was 130/70 mm. Hg. No rash was noted on the skin; the pharynx was not injected. The heart was of normal size. The heart tones were loud, and a diastolic gallop was present. A Grade 2 systolic ejection murmur was heard at the pulmonic area, preceded by an early systolic click. A Grade 1 apical mid-diastolic rumble was also present. No variation in the first heart tone was noted at the time of admission. Tenderness and swelling were present in the region of the right ankle. The rest of the physical findings were noncontributory.

Laboratory data. A blood count showed 3,460,000 erythrocytes, hemoglobin of 9.8 Gm., 10,400 white blood cells, of which 65 per cent were polys, 20 per cent bands, 11 per cent lymphocytes, and 4 per cent monocytes. Sedimentation rate was 56 mm. The urinalysis was normal. Throat and blood cultures, and three lupus erythematosus preparations were all negative. Electrolytes, fasting blood sugar, and blood urea nitrogen were not remarkable. Antistreptolysin-O titer and C-reactive protein at the time of the patient's admission were 250 Todd units and 4-plus, respectively.

Roentgenographic examination of the chest revealed the heart and lungs to be within normal limits. The electrocardiograms are discussed below.

Hospital course. The patient was started on 100 mg. of cortisone, three times a day, and within 12

From the Department of Medicine, Cook County Hospital, and the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago, Ill.
Aided by a National Heart Institute Grant (H2276).
Received for publication July 5, 1960.

hours after admission all pain in the joints and swelling had disappeared. Within 36 hours the patient became afebrile and remained so throughout his entire hospital course. The patient was also started on daily procaine penicillin, 600,000 units, and at the end of 2 weeks was placed on Bicillin. After 2 weeks of therapy, the sedimentation rate had dropped to 14 mm., and the abnormal auscultatory findings of the heart disappeared. Repeat antistreptolysin-O titer and C-reactive protein at this time were still 250 and 1-plus. The final diagnosis was rheumatic fever with active myocarditis.

Electrocardiograms

The first electrocardiogram was obtained before therapy was started. The only abnormality noted was a disturbance of rhythm, illustrated in Fig. 1. The sinus rate varies between 65 and 88 per minute, and there are three types of ventricular complexes, all with a normal QRS duration of 0.08 second. The first, with small QRS and an inverted T wave, is linked to P waves at a constant prolonged P-R interval of 0.24 second (first three beats in strip *a*, and second and third beat in strip *d*). These occur during atrial rates of 77 to 88 and represent fully conducted sinus impulses. The second type, with large QRS complexes and upright T waves, has no constant relation to P waves; the latter either precede QRS at a short variable distance (as in strips *a* and *c*) or coincide with it (as in strip *b*). These represent impulses of an accelerated subsidiary pacemaker which is discharging at a precisely regular rate of 67 and interferes in the A-V junction with sinus impulses whenever the rate of the latter has slowed to 68 or more. The result is an "isorhythmic" A-V dissociation. The third type (fifth to seventh beats in strip *d*) follows P waves at the same P-R interval as the sinus beats but is intermediate in shape between the other two types. These beats occur during sinus rates of 70 or 71 and represent ventricular fusion beats due to interference of sinus and ectopic impulses within the ventricles. Their significance with regard to the location of the ectopic pacemaker is discussed below.

On the following day, isorhythmic A-V dissociation was still present but at a slower rate of 58 (Fig. 2,*a*). On the third hospital day the sinus rate varied between 44 and 65 but the accelerated ectopic activity had subsided (Fig. 2,*b*). Consequently, all sinus impulses were conducted at a prolonged P-R of 0.24 second. Subsequent electrocardiograms showed gradual regression of the A-V conduction disturbance, and on the eleventh hospital day the tracing was normal with a P-R of 0.14 second (Fig. 2,*c*).

This series of electrocardiograms revealed, therefore, a first-degree A-V block, at first in conjunction with an intermittent and isorhythmic type of A-V dissociation induced in a sinus arrhythmia by temporary acceleration of a subsidiary ectopic pacemaker. The location of the latter is discussed below. Both these abnormalities disappeared with clinical improvement of the patient.

Discussion

The term *A-V dissociation* in its broadest sense comprises disturbances of cardiac rhythm characterized by independent action of atria and ventricles. Its several varieties are subject to different classifications, depending on whether they are viewed from the standpoint of *duration*, of *completeness*, or of the *mechanisms* responsible for the disturbance.[3] Thus, in a given record, the A-V dissociation may be persistent or it may alternate with longer periods of normal rhythm (intermittent variety). On the other hand, persistent as well as intermittent A-V dissociation may be incomplete or complete, in that a regular sequence of the ectopic beats may or may not be disturbed by atrial impulses sporadically traversing, or penetrating to, the point of origin of the ectopic pacemaker (ventricular captures). Finally, from the viewpoint of mechanisms, persistent or intermittent, complete or incomplete, A-V dissociation may be the result of either (a) delay in arrival of the atrial impulses or (b) early discharges of a subsidiary center.[4] The former "passive" mechanism may result from sinus bradycardia or an S-A or A-V block; the latter "active" one occurs in a paroxysmal and nonparoxysmal variety distinguished by the type of onset and termination as well as by the degree of acceleration of ectopic impulse formation.[5]

In acute rheumatic fever, the most common cause of A-V dissociation is a nonparoxysmal A-V nodal tachycardia. It is a highly significant finding and has the same clinical connotations with regard to involvement of the myocardium, specifically

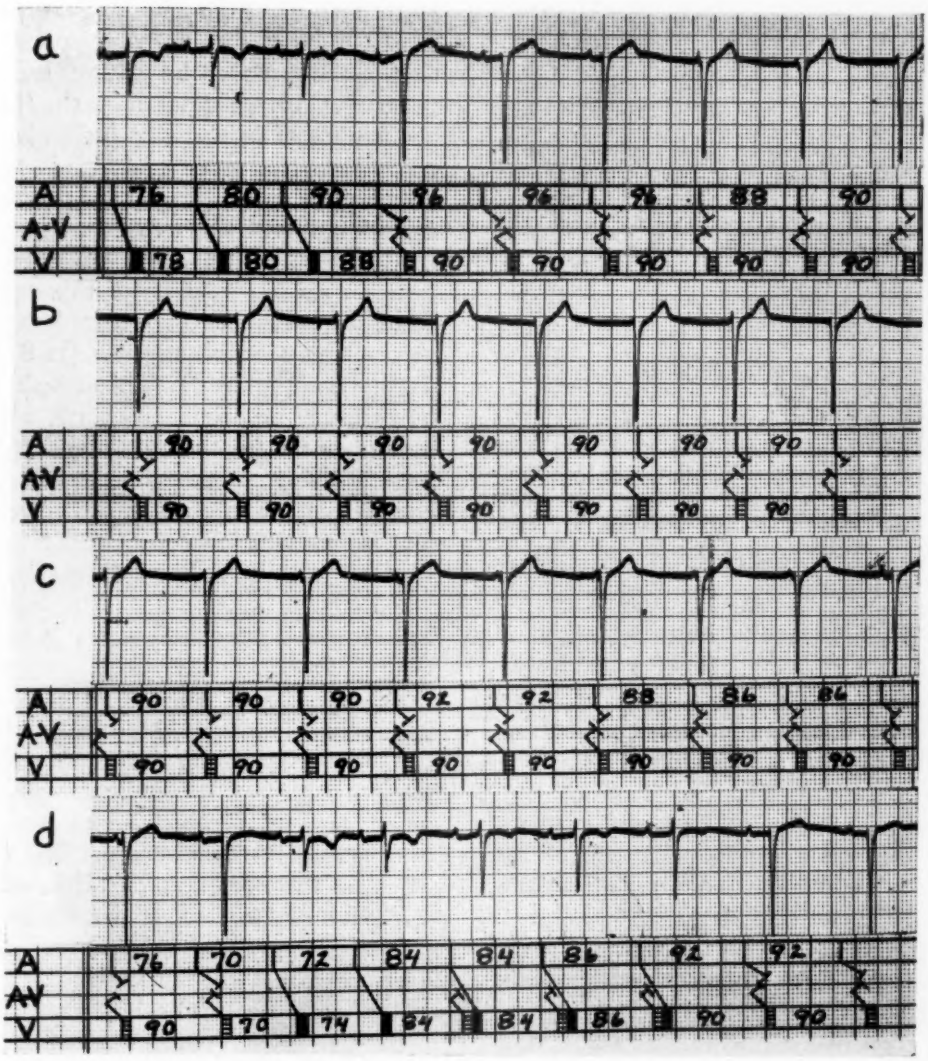

Fig. *1*. Electrocardiogram at the time of admission (April 23, 1960). Segments *a-d* are consecutive portions of a long Lead V_1, with only a few beats omitted between the individual strips. The symbols in the diagrams are conventional. The solid blocks under *V* represent ventricular activation by sinus impulses; the shaded blocks, activation by ectopic impulses which originate within the A-V node and use a preferential path to the ventricles; their combination indicates ventricular fusion beats. Discussed in text.

the A-V node, by the underlying rheumatic disease as does a prolongation of the A-V conduction time. These two functional disorders may or may not be associated. They differ in that, as a rule, acceleration in nodal impulse formation is more transient than the delay in A-V conduction. Whether under these circumstances the A-V dissociation is persistent or intermittent, or is complete or incomplete, will depend on the degree of nodal acceleration relative to the rate and rhythmicity of the sinus node and the state of refractoriness of the A-V node. Since in nonparoxysmal tachycardias, acceleration of ectopic impulse formation is only moderate and remains within the range of sinus rhythms, there is frequently transient or persistent synchronization of the two rhythms. This phenomenon is known as *isorhythmic dissociation* or *accrochage*.[6] There is reason to doubt whether the mechanism of accrochage as conceived by Segers[2] is actually demonstrable in the human heart. Grant[7] reproduced the phenomenon experimentally and demonstrated a "pull in" of two coupled oscillators operating originally at two different rates. He concluded that such

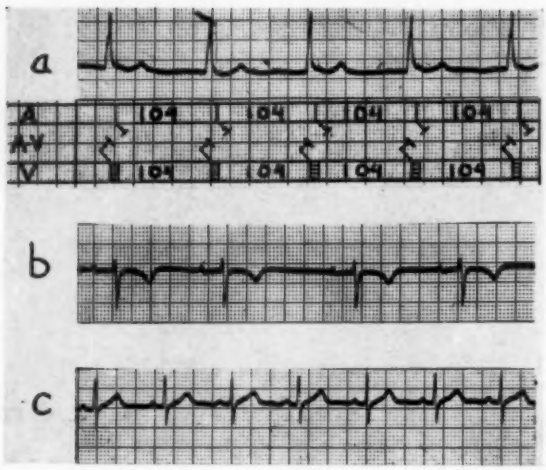

Fig. *2*. Electrocardiograms after therapy. Discussed in text. *a*, Lead III taken on April 24. *b*, Lead V_1 taken on April 25. *c*, Lead I taken on May 8.

physical principles can be applied to explain various manifestations of nodal arrhythmia, including accrochage. However, it is possible that temporary synchronization may simply be the result of chance acceleration of ectopic impulse formation to, but not beyond, the range of a pre-existent arrhythmia of the sinus pacemaker. Such an interpretation can readily be applied to the present case, since the apparent linkage of the two pacemakers (Fig. 1,*b*) is immediately broken as soon as the sinus rate speeds up (Fig. 1,*d*).

The interpretation of complexes 5, 6, and 7 in *d* of Fig. 1 as being ventricular fusion beats is based on the following facts: (a) They are intermediate in contour between the sinus and ectopic beats. (b) These beats occur exclusively at the time of sinus slowing when the appearance or disappearance of ectopic beats can be predicted. (c) The cycle of these beats is either equal to, or only 0.04 second shorter than, the regular ectopic cycle. (d) Each of these beats is preceded by a P wave with the same P-R interval as seen in the normally conducted beats. Yet the identification of these beats as ventricular fusion beats creates one difficulty, namely, that of establishing the location of the ectopic pacemaker—the most intriguing aspect of the tracing.

Ventricular fusion beats are the result of interference at ventricular levels of two activation waves.[3] Obviously, this cannot take place if the two impulses share a common path through the A-V junction. At least one must originate below the bifurcation of the common bundle or else reach the ventricles over a devious path. Hence, the occurrence of ventricular fusion beats in an ectopic rhythm with prolonged and bizarre ventricular complexes can ordinarily be considered as strong evidence of a ventricular location of the ectopic center.[8] However, in the application of this criterion to the case presented, the problem arises of accounting for the normal QRS duration of the ectopic beats. This dilemma could be resolved on the basis of two alternative assumptions: (a) the ectopic impulses originate in the A-V junction but use a preferential pathway in reaching the ventricles,[9] or (b) they originate within the ventricular septum about midway between the two bundle branches.[3] Either of these two mechanisms could conceivably result in aberrant ventricular beats with a normal QRS duration. We are unable to distinguish conclusively between these two possibilities, but we favor, for empirical reasons, the first interpretation (indicated in the diagrams to Fig. 1), since acceleration of A-V nodal, and not ventricular, impulse formation is the common manifestation of involvement of the heart muscle in an acute rheumatic process,[5] as was present in this case.

It should be emphasized that this recognition of the occurrence of ventricular fusion beats in the face of a supraventricular ectopic rhythm does not of necessity conflict with the foregoing statement concerning the crucial role of fusion beats in the distinction between ventricular and supraventricular ectopic beats. This criterion appears to be diagnostic if the QRS duration of ectopic beats of questionable origin exceeds 0.12 second.

Summary and conclusions

1. We have reported a case of active rheumatic myocarditis which was revealed by two functional manifestations of a pathologic process involving the atrioventricular junctional tissue: a nonparoxysmal A-V nodal tachycardia and impairment of A-V conduction which resulted in intermittent "isorhythmic" A-V dissociation.

2. A-V dissociation always started with slowing of the sinus pacemaker and

promptly disappeared with its acceleration. Temporary synchronization of atrial and ventricular action appeared to be a chance phenomenon which depended on a sinus arrhythmia, rather than the result of a "pull in" (accrochage) of two rhythms differing in rate, a mechanism implied by others.

3. The ventricular complexes of the ectopic rhythm differed markedly from those of sinus origin in contour, but not in QRS duration. Considering the known affinity of the rheumatic process to A-V junctional tissues, we assume that the site of this ectopic pacemaker was above the bifurcation of the common bundle, probably in the A-V node, and we attribute the aberration in contour to a "preferential" conduction path to the ventricles.

4. At the transition of the undisturbed sinus rhythm into A-V dissociation, and vice versa, there was competition between sinus and ectopic impulses for control of the ventricles, which caused ventricular fusion beats. The significance of the latter in the difficult distinction between supraventricular and ventricular beats is reevaluated.

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Hypotension accompanying ECG changes in two uremic patients with severe hypocalcemia

*A. M. van Leeuwen**
L. W. St. van Eps, M.D.§*
*S. T. Boen, M.D.**
*R. J. Vroom***
Amsterdam, Netherlands

Clinical observations on the influence of hypocalcemia on the heart are nearly all concerned with the effect on the ECG only.

However, Strawitz and associates[1] observed an immediate improvement in the arterial pressure after intravenous injection of 1 to 2 Gm. of calcium gluconate (4-9 milliequivalents calcium in 4 patients who developed severe hypotension during massive transfusion of citrated blood. The blood chemistry is not mentioned and no ECG was made, but the authors conclude that overdosage of citrate was responsible for a sharp decrease in the ionized plasma Ca, which, in turn, caused hypotension.

Clowes and Simeone[2] found a decrease—often marked—in the concentration of ionized plasma calcium during major operations. Severe hypotension occurred in 4 patients with levels of ionized plasma calcium below 1.6 mEq. per liter. In 2 patients, 1 Gm. of $CaCl_2$ (about 20 mEq. of Ca) given intravenously resulted in a dramatic return of the arterial pressure to normal, whereas a blood transfusion had not been successful. No further details are given, but the authors stress the importance of too low a level of ionized plasma calcium as a cause of hypotension.

Merrill and associates,[3] in an article on recognition and treatment of potassium intoxication, mention a patient (Case 5) with oliguria and hyperkalemia in whom intravenous injection of 3 Gm. of $CaCl_2$ (about 60 mEq. of Ca) was followed by an increase in systolic blood pressure from 120 to 200 mm. Hg, a disappearance of gallop rhythm, and some improvement in the typically hyperpotassemic ECG. Serum Ca rose from 3.4 to 5.9 mEq. per liter, and potassium was—after the infusion—7.0 mEq. per liter. The observation is not further documented, but the authors observe that "the change in serum calcium level may have played a role" (in combating the toxic effect of hyperpotassemia).

In 2 uremic patients with severe hypocalcemia, we observed that hypotension accompanied the typical ECG abnormality. In the 2 patients, both the arterial pressure and the ECG were normalized by raising the plasma calcium to the normal level.

From the University Department of Medicine, Binnengasthuis, Amsterdam, Netherlands.
Received for publication July 15, 1960.
*Head Assistant, University Department of Medicine, Binnengasthuis.
**Assistant, University Department of Medicine, Binnengasthuis.
§Supported by a grant from the Government of the Island Territory of Curacao.

Methods

All chemical determinations were done in duplicate. Methods used were: Ca and Mg—photoelectric titration with complexon III[4]); Na and K—flame photometer; total protein—biuret method[5]; protein fractions —according to Majoor.[6]

ECG tracings were made with a Sanborn Visocardiette. The Q-T interval was measured from the beginning of the Q to the end of the T wave, with an accuracy of within 0.01 second. The values subsequently given for the Q-T intervals represent the average of 4 to 6 measurements on consecutive cardiac cycles of Lead I. The differences between the Q-T intervals of the various leads were in no instance larger than 0.02 second.

Case histories

Case 1. Patient K.H., a 28-year-old man, went to Surinam (West Indies) in September, 1956. On November 11, during the homeward journey, he had a severe attack of tropical malaria, followed by an acute anuria. Because of hyperkalemia and lung edema, peritoneal dialysis was performed elsewhere, the application of cuffs around the thighs for 36 hours having had no effect.

Hyperkalemia and lung edema disappeared, but the patient remained apathetic and the anuria persisted.

On December 2, the third day after the peritoneal dialysis, a paresis of the legs became manifest, together with absence of the tendon reflexes. This could not be explained by the level of plasma potassium (5.4 mEq./L.). No sensory disturbances were noted. The ECG showed a sinus tachycardia with definite prolongation of the Q-T interval: hypocalcemia was suggested by Dr. A.P.M. Verheugt, the consulting cardiologist. The blood pressure, which had been normal, started to drop, and that same evening, at 5 P.M., the patient was transferred to our department, in a state of shock, with a blood pressure of 80/60 mm. Hg, a regular pulse rate of 105, and a pronounced triple rhythm. The heart was not enlarged on percussion, and there were no signs of lung edema or peripheral edema. Chvostek's sign was absent; the paresis of the lower limbs had become marked.

Because of the peculiar flaccid paresis of the lower limbs, 25 mg. of thiamine chloride intramuscularly was given tentatively at 6 P.M. Blood analysis, however, confirmed the diagnosis of Dr. Verheugt and revealed a severe hypocalcemia (2.1 mEq./L.), as well as hyperphosphatemia (18 mg. per cent) and uremia (4 Gm./L.). The other electrolytes were not noticeably abnormal (Fig. 1, *Observation 1*).

It was then decided to try the intravenous administration of Ca, and an infusion of Ca gluconate (44 mEq. of Ca in 510 ml. of 5 per cent glucose) was started at 11 P.M. The beneficial effect on the plasma Ca, ECG, blood pressure, and triple rhythm is shown in Fig. 1, *Observation 1*, and will be discussed later.

Parallel with the improvement in the level of plasma Ca, active movement of the legs also returned. The tendon reflexes could be elicited again 2 hours after the start of the administration of Ca.

In the course of the following days, diuresis gradually set in, and ultimately the patient recovered completely. No further thiamine was given. Administration of Ca, however, had to be continued in quantities up to 80 mEq. daily for another 2 weeks, in order to prevent hypocalcemia. No further circulatory or neurological abnormalities were noted. The effect of peritoneal dialysis and the course of the renal failure in this patient have been reported elsewhere.[7] The moderate hypocalcemia (3.5 mEq./L.) which existed before dialysis was aggravated presumably by a low concentration of Ca ion in the irrigation fluid, due to precipitation of $CaCO_3$. The rise in the plasma phosphate during the days following the dialysis induced a further decrease in the plasma calcium.

Case 2. Patient St., a 22-year-old married woman who had a history of tonsillitis and acute glomerulonephritis 4 years previously, visited a hospital elsewhere in November, 1958, because of increasing complaints of vomiting and epistaxis. Severe uremia (blood urea 4,000 mg./L.) with anemia resulting from chronic glomerulonephritis was diagnosed. At that time the blood pressure was 170/120 mm. Hg.

Vomiting persisted, and on Dec. 27, 1958, she was admitted to our department.

The blood pressure was then 110/80 mm. Hg, which contrasted sharply with the hypertension found previously. The pulse rate was 80 to 90 and regular. There were no signs of dehydration, but, on the contrary, slight edema. This could not be due to a low content of albumin (albumin: 31 Gm./L.; total protein, 58 Gm./L.).

The heart was not enlarged on percussion, and there was no triple rhythm. Chvostek's sign was positive, but there were no other neurological abnormalities and no history of manifest tetany. There was no paresis of the limbs, and the patient, although ill, was mentally alert. The ECG showed a sinus rhythm with prolongation of the Q-T interval.

The blood chemistry (see *Observation 2*, Fig. 1) revealed severe uremia with pronounced hypocalcemia (2.3 mEq./L.) and hyperphosphatemia (23.6 mg. per cent). The level of potassium was only slightly raised (5.2 mEq./L.), and there was a mild metabolic acidosis (HCO_3 concentration; 16.0 mEq./L.).

The creatinine clearance was extremely low (2 to 3 ml./min.), and the diuresis remained fixed at about 1 liter in 24 hours, with an excretion of albumin of 4 Gm. daily. The excretion of Ca was not determined.

Immediately after the patient was admitted to the hospital, an infusion of calcium gluconate (44 mEq. of Ca in 600 ml. of 5 per cent glucose) was started. This resulted in a normalization of the ECG and a concomitant rise in blood pressure. The general condition improved considerably. The correlation with the level of plasma calcium is shown in Fig. 1, *Observation 2*.

Clinical improvement, however, was temporary, and after 2 days the plasma calcium had dropped to the same low level, the blood pressure had fallen,

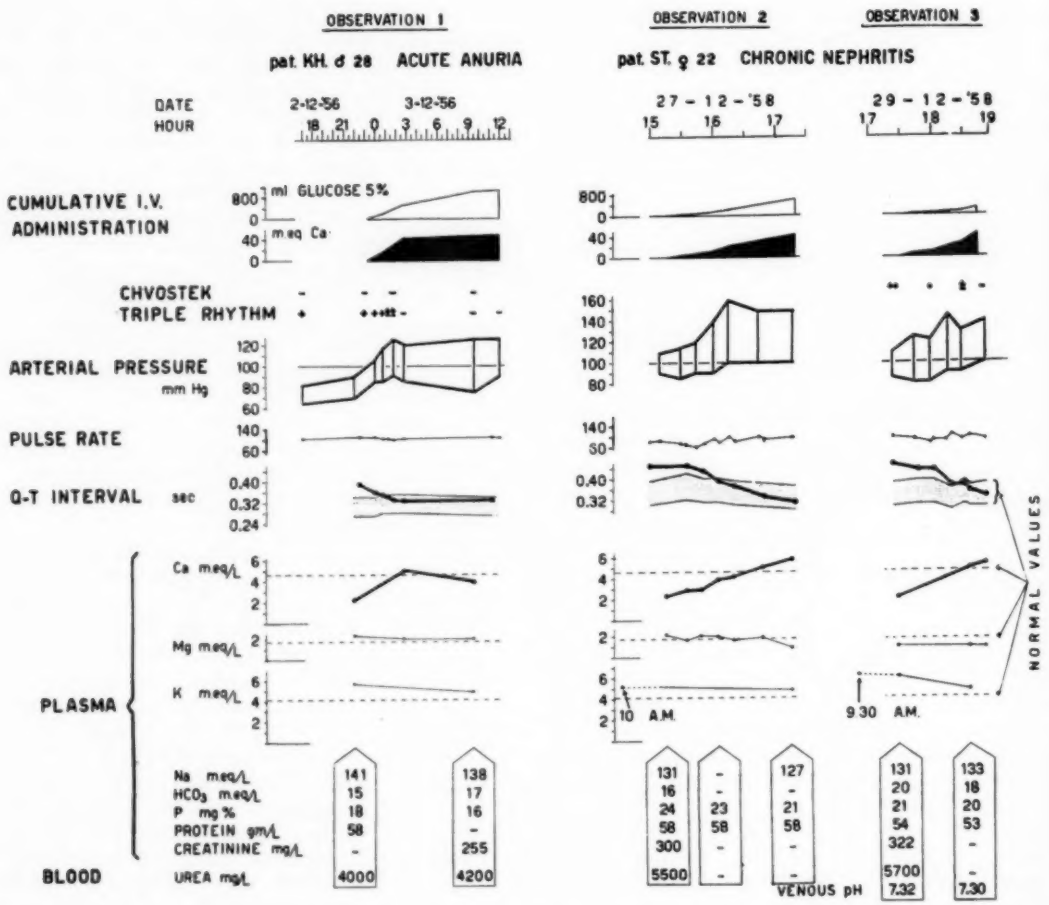

Fig. *1*. Graphic representation of observations in Patient K.H. and Patient St. The normal range for the Q-T interval was taken from the *Electrocardiographic Test Book* of the American Heart Association.[9] The mean normal values indicated for the magnesium and potassium in plasma are the values found for normal persons in our department. For Ca this value is corrected for the deviation of total plasma protein in our patients from 70 Gm./L., using the formula of McLean and Hastings.[11]

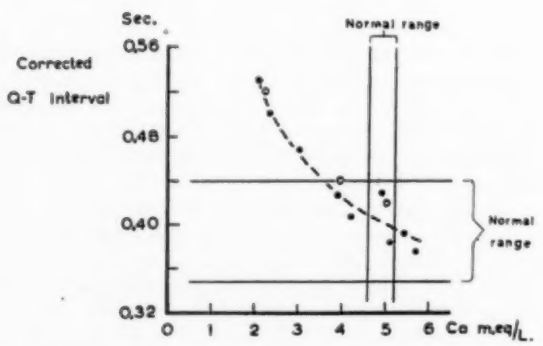

Fig. *2*. Correlation between the concentration of calcium in the plasma and the corrected Q-T interval (Kissin and co-workers[8]). Solid dots: Patient K.H. (*Observation 1*). Open dots: Patient St. (*Observations 2 and 3*). The broken line indicates the general trend and has no statistical significance. The normal range for corrected Q-T interval in adults was taken from the *Electrocardiographic Test Book* of the American Heart Association.[10]

and the ECG again revealed the typical abnormality, notwithstanding the administration of 20 mEq. of calcium and a large amount of fluid (2,500 ml. of 20 per cent glucose) intravenously on December 28. A second rapid infusion of calcium gluconate (44 mEq. of Ca in 220 ml. of 5 per cent glucose) again had a beneficial effect (see Fig. 1, *Observation 3*). This time Chvostek's sign was repeatedly looked for and was found to disappear gradually with the normalization of the plasma calcium.

The patient was treated with calcium gluconate and infusions of glucose, vitamin D, oral calcium, Aluminox (which is a 5 per cent $Al(OH)_3$ gel), and a low-protein diet, but the uremia rapidly increased and she died on Jan. 19, 1959. At autopsy a severely contracted right kidney and a hypoplastic left kidney with hypoplastic renal artery were found.

An extremely high concentration of inorganic phosphate in the plasma in combination with insufficient compensatory activity of the parathyroid glands might have been responsible for the persistent hypocalcemia in this patient.

Effect of administration of Ca on blood pressure, ECG, and blood chemistry

In Fig. 1 the effect of infusion of Ca gluconate on the clinical signs, blood pressure, Q-T interval, and blood chemistry is shown. In all three observations a correlation exists between the level of Ca in the plasma, Q-T interval, and blood pressure. The blood pressure became stabilized at the normal level for the patient as soon as the plasma Ca had become normal. At that moment the Q-T interval had also come within a normal range: in all three observations, about 20 mEq. of Ca had been given until then. The rise in plasma Ca above the normal level seen during *Observation 2* is accompanied by a continuing decrease in the Q-T interval, but not by a further increase in blood pressure.

In Fig. 2 the concentration of plasma calcium and the Q-T interval (corrected to a heart rate of 60 per minute, using the nomogram of Kissin and co-workers[8]) are correlated. Only with plasma concentrations below 3.5 mEq./L. did the Q-T interval become significantly prolonged.

Fig. 3 shows serial electrocardiograms of the patients. It should be noted that the prolongation of the Q-T interval is due to a lengthening of the S-T segment. In Patient K.H., an inverted T wave which was seen in Leads I, II, and aV_L became less negative during infusion of calcium; in Leads III, aV_R, and aV_F the T waves were positive, tending to flatten during infusion of calcium. In the second patient the T waves stayed positive.

There was initially in all three observations a slight to moderate hyperkalemia. During administration of Ca, changes in plasma potassium were seen, but these showed no constant pattern: during the first observation a decrease of 0.8 mEq./L. occurred; in the second observation no change was seen, whereas during the third observation a decrease of 1 mEq./L. occurred. The decrease must be attributed to the glucose administered.

The concentration of magnesium which was slightly elevated in Patient K.H. remained constant during the infusions of Ca.

No significant changes were observed in the content of bicarbonate in the plasma (Fig. 1, *Observations 1, 2, 3*), nor in the pH of the venous blood drawn from the resting forearm (Fig. 1, *Observation 3*). The latter value was well within normal range.

Total concentration of protein in the plasma was only slightly below normal, and did not change during the observation period.

Discussion

Before considering the circulatory and electrocardiographic changes, we will comment briefly on the neurological findings. The flaccid paresis of the lower limbs, with absence of tendon reflexes, which was observed only in Patient K.H., is at variance with the known effects of hypocalcemia and might even be called paradoxical. The fact that the administration of Ca promptly restored normal movement and tendon reflexes nevertheless suggests that the hypocalcemia was partially responsible. A contributory mechanical factor may have been the application of cuffs around the thighs for 36 hours, at a pressure of 60 mm. Hg. In Patient St., Chvostek's sign was positive, but there was no manifest tetany although the concentration of Ca ion in the plasma must have been very low. Strawitz and associates[1] and Clowes and Simeone[2] also observed no signs of tetany, notwithstanding the low levels of Ca ion in the plasma. We have no explanation for this lack of nervous hyperexcitability.

It is improbable that the administration of 25 mg. of thiamine chloride intramuscularly was responsible for the sudden and lasting improvement in Patient K.H. 6 hours later. The patient had always had an adequate diet and was not an alcoholic. The neurological and circulatory disturbances developed within 2 days, without an evident increase in demand for thiamine. Finally, although shock and prolongation of the Q-T interval have been described in cases of thiamine deficiency, the improvement both in the circulation and neurological signs occurred in the course of 2 hours and in close correlation with the change in the level of Ca in the plasma (Fig. 1, *Observation 1*, and Fig. 2).

In view of the observation made in Patient St., who received only calcium, a direct relation seems to exist, therefore, between hypocalcemia, prolongation of the

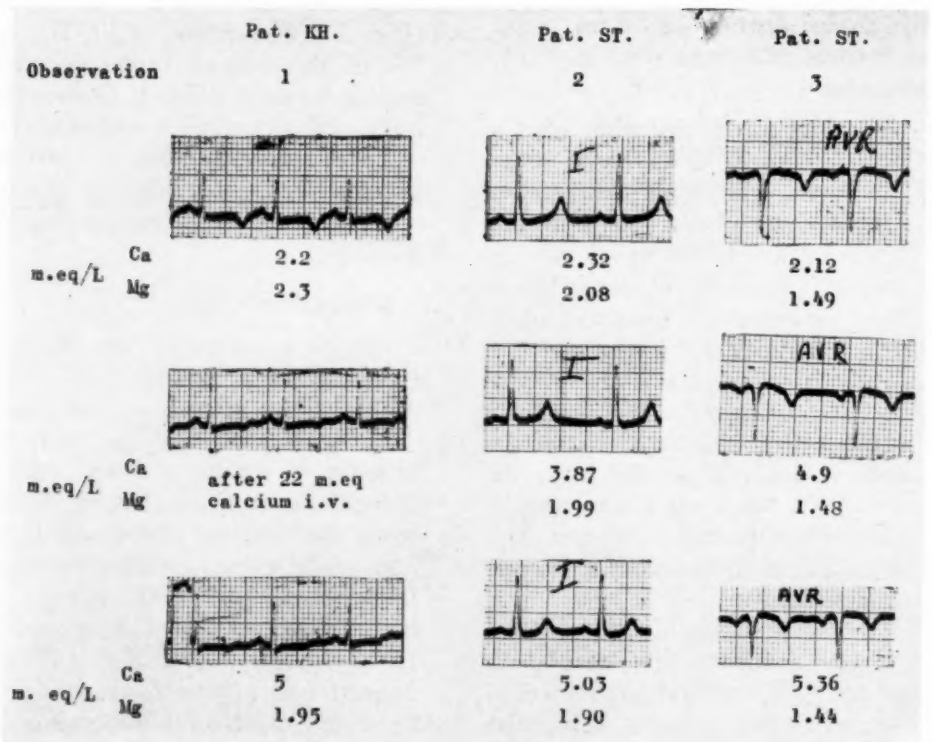

Fig. *3.* Serial electrocardiograms which show normalization of the Q-T interval during administration of calcium. *Observation 1:* Lead I. *Observation 2:* Lead I. *Observation 3:* Lead aV_R.

Q-T interval, and hypotension; and it would appear that the low level of Ca in the plasma—which in the absence of significant abnormalities in the plasma proteins and pH indicates a very low concentration of Ca ion—was responsible not only for the ECG changes but also for the decrease in blood pressure.

From the fact that manifest shock concomitant with triple rhythm developed in Patient K.H., and that both disappeared as the plasma Ca rose to normal levels, it would appear that the effect of hypocalcemia on the arterial blood pressure is due to a decrease in the force of cardiac contraction and not to a diminished peripheral vascular resistance. The amount of fluid administered parenterally is too small to explain the increase in arterial pressure. The level of potassium in the plasma was slightly elevated but did not show a correlation with the increase in arterial pressure, and can, therefore, not account for it.

The outstanding electrocardiographic abnormality was the prolongation of the Q-T interval; such prolongation was first described by Carter and Andrus[12] in 1922, and subsequently by many other authors.[13-19] It is due to a lengthened S-T segment and is now considered to be characteristic of hypocalcemia. The fact that in our patients the Q-T interval became significantly prolonged only at concentrations of Ca below 3.5 mEq./L. (Fig. 2) is in agreement with observations made by others.[13,18]

Bellet[18] occasionally found inverted T waves during hypocalcemia. These became less negative after the administration of Ca. Similar alterations in the T wave were seen in Patient K.H. (Fig. 3).

With the exception of that cited in the introduction, the clinical literature on hypocalcemia does not mention observations on cardiac function or arterial pressure. But experiments on the isolated heart support the assumption that hypotension in cases of hypocalcemia is caused by a diminished force of cardiac contraction.[20,21] Under standardized conditions the force of contraction of the frog heart can be used as a measure of the concentration of Ca ion in the perfusion fluid, and it is interesting to note that the isolated frog heart is most sensitive to small changes if the

concentration of Ca is low. At normal and high concentrations, changes in the level of Ca ion do not appreciably influence the force of contraction.[21,22]

The same pattern can be observed in *Observation 2*, Fig. 1. The most impressive rise in blood pressure occurred immediately after the concentration of Ca started to rise, and an increase of the level of Ca in the serum above the normal level did not further increase the arterial blood pressure.

The observations of Strawitz and associates[1] and Clowes and Simeone[2] and our observation can be said to demonstrate a digitalis-like action of Ca on the force of cardiac contraction in cases of hypocalcemia. It is of interest, therefore, that other workers found evidence for a synergistic or additive action between Ca and digitalis glycosides in experiments on the isolated heart,[20,22,23] on intact animals,[24] and in clinical observations.[25-29] The evidence put forward in the publications just referred to is often too circumstantial or lacking in facts, and quite a number of authors have refuted the proposed synergistic or additive action between Ca and digitalis glycosides, on the grounds that an increase in the level of Ca in the plasma above the normal level does not significantly increase the toxicity of the digitalis preparations administered.[30]

We think that in these experiments—as in the experiments on the isolated frog heart—the absolute level of plasma Ca, or, to be more accurate, Ca ion, is decisive. This is clearly shown in the publication of Friedman and Bine,[31] who from their experiments on the embryonic duck heart concluded that Ca had no influence upon the action of a digitalis glycoside. However, when Ca was omitted from the perfusion fluid, the hearts were significantly more resistant to the digitalis glycoside used than when the perfusion fluid contained about 4 mEq./L. of Ca. An increase in the content of Ca above that level had no effect. Rohrer[22] demonstrated a similar dependency of the digitalis effect on the absolute level of Ca in the isolated frog heart.

It seems, therefore, that a similarity exists between the effect of digitalis and of Ca on the heart, and Szent Görgyi[32] suggested that this is due to the fact that Ca blocks the mechanism responsible for transport of potassium into the cell, in the same manner as do the cardiac glycosides.

Whether this is true or not,[22] it has long been known that the effect of Ca on isolated heart muscle is influenced by the concomitant concentration of potassium; diminished force of contraction is seen only with hypocalcemia if the concentration of potassium is at least normal.[20,21] If the concentration of potassium in the perfusion fluid is lowered concomitantly with the concentration of Ca, the force of contraction of an isolated frog heart remains normal.[33]

The 4 patients with severe hypocalcemia and hypotension mentioned by Clowes and Simeone[2] all had a slightly elevated potassium. The same was found in our patients. The patient observed by Merrill et al.[3] had a moderate hypocalcemia, but was frankly hyperpotassemic. It will be interesting to study circulatory changes after the administration of Ca and potassium, respectively, in patients who have both a low level of Ca and potassium in the plasma.

Summary

Three observations in 2 uremic patients with severe hypocalcemia are described.

1. Besides prolongation of the Q-T interval, severe hypotension was found.

2. During intravenous administration of calcium the blood pressure rose, and the Q-T interval was normalized concomitant with the increase of the concentration of plasma calcium to its normal level; when in the second patient the concentration of Ca again diminished, hypotension and prolongation of the Q-T interval reappeared.

3. In the first patient a triple rhythm was present during hypocalcemia, but disappeared during administration of Ca. A flaccid paresis of short duration of the lower limbs existed, but also disappeared completely during administration of Ca. Chvostek's sign was consistently negative.

4. The conclusion is that in these cases, hypocalcemia was responsible for the hypotension, probably by decreasing the force of cardiac contraction. The slightly elevated level of potassium found in all three observations may have been a contributory factor.

5. Since others have made similar observations after massive transfusion of citrated blood, and during major operations, the possibility of hypocalcemia should be considered in patients with hypotension refractory to adequate transfusion. The finding of a prolonged Q-T interval due to lengthening of the S-T segment is then of diagnostic importance, since the classic neurological signs of hypocalcemia may be absent.

Addendum

After this paper had been submitted for publication, a fourth observation was made in Patient Fr., a 52-year-old woman who suffered from chronic renal insufficiency, which probably resulted from pyelonephritis.

When she was first admitted in 1959, the nephritis was found to be of the salt-losing type. Arterial pressure varied between 170/110 and 210/130 mm. Hg, plasma sodium between 118 and 135 mEq./L., and endogenous creatinine clearance between 5 and 11 ml./min. Plasma calcium then was 3.5 mEq./L.

In August, 1960, she was readmitted in a severely overhydrated state, with an arterial pressure of 160/100 mm.Hg. With the intake of fluids and salt restricted the overhydration disappeared and plasma sodium fell from 135 to 118 mEq./L. After a few weeks, however, arterial pressure gradually fell to 120/70 mm.Hg, and the triple rhythm returned. A slow infusion of 150 ml. of NaCl, 0.6 per cent, did not raise the arterial pressure, although it increased central venous pressure. Plasma calcium was then found to be 2.3 mEq./L., and the Q-T time was prolonged. With the administration of calcium lactate orally the plasma calcium rose in one week to 2.9 mEq./L., and arterial pressure to 140/80 mm.Hg; the triple rhythm diminished but did not disappear and plasma sodium had come down to 112 mEq./L. The patient was then given 44 mEq. of calcium gluconate in 200 ml. of 0.25 per cent glucose in the course of 92 minutes, and the same effect was observed as in the first three observations (see Table I). It should be noted that, in this case, potassium was within the normal range and did not change.

The low concentration of sodium might have contributed to the development of hypotension, as suggested by Merrill and associates,[3] although in the in vitro experiments a low concentration of sodium appears to enhance rather than decrease the effect of calcium ions on the contraction force of the frog heart.[20,34]

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Table I

	14 hr.	*Ca gluconate infusion*		*18 hr.*
		14 hr. 45	*16 hr. 19*	
		Start	*End*	
Arterial pressure (mm. Hg)	150/85	150/80	185/105	180/90
Triple rhythm	±	±	—	—
Q-T time (sec.)	0.38	0.36	0.28	
Normal range		0.27–0.36		
Ca		2.96	5.36	
Mg		1.58	1.44	
K (mEq./L. plasma)		4.70	4.70	
Na		113	112	
HCO_3		22	22	
Inorganic phosphate (mg.%)		10	10	
Venous pH		7.36	7.37	
Total protein (Gm./L.)		56	55	

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Review

Recent developments in hypertensive therapy

F. H. Smirk, K.B.E., M.D., F.R.C.P., F.R.A.C.P.
Dunedin, New Zealand

Those who began to use modern hypotensive drugs in late 1949 and early 1950, may review some ten and one-half years of experience with potent hypotensive agents. Some information has become available on the effect of reducing high blood pressures, but the extent to which the blood pressure can or should be reduced is still debated. Meanwhile the development of several valuable hypotensive drugs has made it easier to reduce significant side effects. However, even at the present time, to obtain a sufficient reduction of the blood pressure, without side effects, often involves trials with several combinations of drugs. The availability of hexamethonium in 1949, afforded the author the opportunity to test the extent to which an effective reduction of blood pressure could reverse some of the clinical manifestations associated with hypertension.[1] Hexamethonium was administered to severe hypertensive patients by continuous subcutaneous injection over a period of 10 to 14 days so as to maintain normotensive levels. A mechanically operated syringe was used, and the level of the blood pressure was controlled by measurements made at 15-minute intervals throughout the day and occasionally during the night. The results of this acute therapeutic study were dramatic, in that obvious regression of papilledema had set in within 2 weeks, and relief of frank hypertensive heart failure occurred without recourse to diuretics, salt restriction, or digitalis.[2] The hypothesis already held by the author concerning pathogenesis,[3] together with the dramatic improvement seen when the blood pressure was maintained very near to an ideal normal level, through the day and night, led to the conviction that some method should be used to maintain levels of blood pressure as near to this ideal as was practicable and on a long-term basis. Fortunately, the decision was taken to treat patients with high basal blood pressures and Grade II retinal changes, as well as those with more advanced retinopathy, and in these patients also to maintain levels of blood pressure as near to normal as was practicable.

The advent of additional therapeutic agents, by allowing an improvement in the control over levels of blood pressure without increase of side effects, has led to a confirmation of the results obtained earlier by those who were prepared to go all the way with ganglion-blocking drugs alone. It is generally agreed now that the benefits to be obtained with hypotensive drugs are the expression of a reduction of the blood pressure and are not closely related to the particular agent used for this. Furthermore, it seems to be widely accepted that the degree of benefit is related to the degree of control obtained, and that the outlook is less satisfactory in patients whose levels of blood pressure are insufficiently reduced.[4,5]

It is agreed among those who have de-

From the Department of Medicine, University of Otago, Dunedin, New Zealand.
Financial support for this study was received from the Medical Research Council of New Zealand.
Received for publication Aug. 15, 1960.

voted special attention to the subject that most potentially reversible hypertensive manifestations are dispersed or greatly improved by a reduction of blood pressure. Papilledema, retinal edema, hemorrhages, and soft exudates can be removed in most instances within a few months after the institution of an adequate regimen; hard exudates may be removed, also, but often this takes as long as 12 months.[6-13]

Great improvement occurs in cardiac asthma and congestive heart failure,[1,8,12-20] to the extent that many authors state that, since the institution of effective hypotensive therapy, deaths from heart failure have been reduced to a negligible level.[18-20]

When ganglion-blocking drugs and reserpine were the only satisfactory hypotensive agents available, it was the practice in our clinic to demonstrate that in the great majority of patients with cardiac asthma, and in about half of the patients with general congestive heart failure, it was possible, without much delay, to relieve the heart failure or cardiac asthma by use of ganglion-blocking drugs alone, without any other therapeutic agents.[20] Such improvements were usually maintained, which indicates the importance of a continued cardiac overload in the pathogenesis of hypertensive heart failure and cardiac asthma. Treatment often led to a decrease of heart size, and usually a degree of improvement in the electrocardiogram.[21,22] Additionally, agreement is general that, usually, patients with hypertensive headaches or dizziness lose these symptoms. In many instances in which such symptoms persist it is because, in our view, a patient on a ganglion-blocking drug is mistakenly allowed to sleep flat in bed, thus securing a high level of blood pressure at night.

Less attention has been devoted in the literature to the prevention of strokes by a reduction of blood pressure. It is our impression that degrees of control over the level of blood pressure which improved the retinae and reverse hypertensive heart failure may yet be insufficient to prevent the occurrence of cerebral vascular accidents. To do this requires a more continuous and better control over the level of the blood pressure. In our records it is evident that in the days of hexamethonium by injection, intermittent falls of the blood pressure relieved heart failure and reversed retinal changes, but did not decrease the occurrence of stroke. A decrease in the incidence of strokes did not occur until additional agents, such as pentolinium and rauwolfia alkaloids became available. The general impression now is that deaths are reduced in number and the pattern of mortality is different. The proportion of deaths from coronary disease has not been reduced. The picture in regard to renal disease has changed. Several writers believe that the development of uremia as a complication of malignant hypertension has been reduced. We have the same impression, although we have not got a sufficient background of controls. In cases of a less advanced character, it is our impression that many patients with primary renal disease, from some such cause as pyelonephritis, who might have died from heart failure or stroke, live long enough with treatment to develop uremia. In our Grade-II and Grade-III patients, particularly the latter, the incidence of deaths from uremia as a percentage total of deaths has increased. The incidence of deaths from uremia as a percentage of patients exposed to risk does not appear to have risen above the level observed in controls.

It is generally agreed that the mortality from malignant hypertension and congestive heart failure has been reduced. Many authors, however, are unwilling to apply hypotensive therapy to less extreme cases. For this there seems to be two reasons: first, some authors appear to consider that a hypotensive regimen involves a patient in so much distress that it is unreasonable to subject him to it except in the presence of advanced disease. In this respect, my view has always been that in the majority of patients it was possible to construct a tolerable regimen, and this aim is more regularly and easily achieved at the present time than it was several years ago. The avoidance of side effects is a matter of technical knowledge and persistence. If a reduction of blood pressure is desirable in moderately hypertensive patients, then from the standpoint of comfort there is no reason why this should not be undertaken.

Examples are often quoted of hypertensive patients who live many years without treatment. It would be of value to be able

to distinguish these more fortunate persons from those who have a high expectation of death or disability from stroke or heart failure. For many years before effective hypotensive therapy was practicable we measured the basal blood pressure routinely by a standard technique.[23] The outlook for untreated patients appears to be related closely to the basal blood pressure, and hardly related at all to the labile fraction of the blood pressure which we have called "the supplemental blood pressure." Our practice has been to treat symptomless patients whose basal blood pressure was sufficiently high, and in general to abstain from treating those whose basal blood pressure fell to a near-normal level. In this connection it should be remembered that the normal range for basal blood pressures by the technique used is very much lower than for casual blood pressures. In general, we consider that there is a strong indication to treat female patients whose basal blood pressure is in excess of 155/90 mm. Hg, and males whose basal blood pressure is above 145/85 mm. Hg. Certainly in our follow-up study, the mortality in untreated persons begins to rise more steeply after these levels.[24]

The follow-up of the first 8 years of our experience in treating Grade-II hypertensive patients has yielded results which are now statistically significant. It appears that the mortality of Grade-II patients who are on hypotensive therapy is approximately half that of corresponding Grade-II patients or patients with slightly milder hypertension who have not had treatment ($p<0.001$).

The question whether something that might be described as preventive treatment should be administered is much in dispute. Our findings indicate clearly that of patients on treatment, very few, if any, develop malignant hypertension. Furthermore, apart from patients who have advanced renal disease, very few develop congestive heart failure, and since 1953, the occurrence of strokes has diminished. The impression, therefore, is that such manifestations of hypertension are to some degree preventable. It is likely that the incidence of heart failure, stroke, and malignant hypertension can be diminished in patients with symptomless high blood pressure, and that, therefore, whenever the level of the blood pressure has risen to within the range at which such manifestations are likely to occur, preventive therapy should be applied. Whether in those patients with very mild hypertension who have casual blood pressures in the region of 160/90 mm. Hg, one should start by reducing the blood pressure is a matter concerning which there is legitimate ground for differences of opinion. My view would be that there is something to be said for maintaining such blood pressures in the fully normal range, provided that any drugs given do not produce side effects.

Preliminary approach to establishing a hypotensive regimen

Good reduction of blood pressure with few side effects depends upon adjusting the regimen to the responses of the individual patients. The procedures involved may be divided conveniently into preliminary measures by which the blood pressure is reduced, followed by a second stage in which adjustments are made to better the regimen by reducing side effects and effecting further improvements in the control over the levels of blood pressure. The initial approach will vary according to the urgency or mildness of the case, and whether the patient can be under all-day supervision during the induction of therapy. Most of our patients attend a day clinic where blood pressures may be measured throughout the day, and the effects of adjustments of dosage on the levels of blood pressure and the side effects are recorded.

One may divide drugs broadly into those suitable for background therapy, such as rauwolfia alkaloids and the hypotensive diuretics, and the more powerful drugs which may be described as the "gravity-augmented hypotensive drugs," which depend for their action on interference with homeostatic circulatory reflexes, and which, in consequence, are associated with postural hypotension. There is no single ideal hypotensive drug, and in the majority of patients the most suitable therapy is by a combination of drugs.

Background therapy. There are some mild cases in which background therapy alone is sufficient to reduce the blood pressure to a satisfactory level: ideally, to between 120/75 and 140/85 mm. Hg for as much of the

24-hour day as is practicable. In mild cases, therefore, there is no objection to observing the effect of background therapy alone, but in severe cases it is desirable to establish a good regimen as soon as practicable, and one may start simultaneously with background therapy and one of the more powerful drugs, the dose of the latter being increased by small amounts daily or even twice daily until the blood pressure begins to approach the desired level.

Perhaps the most satisfactory single drug for background therapy at the present time is hydrochlorothiazide, 50 mg. night and morning, with 5 grains of potassium chloride thrice daily. Hydrochlorothiazide is preferable to chlorothiazide, in that there are fewer side effects. It has had a longer period of clinical trial than hydroflumethiazide, which is approximately of equal potency. A most interesting development is the drug chlormethiazide (Fluitran), which is at least ten times as potent as hydrochlorothiazide and may be used in doses as low as 2 to 4 mg. twice daily. Potassium chloride, 1 Gm. daily, should be given with this drug, at least until it is found whether such supplements are necessary.

If only one drug were to be used for background therapy, I should prefer a hypotensive diuretic to a rauwolfia alkaloid, because, even in doses which cause no mental depression, rauwolfia alkaloids sometimes cause states of mental inertia and apathy, and patients who make no specific complaint about side effects may feel better without them. Such a statement does not apply to all or even a majority of patients. Many take small doses of rauwolfia alkaloids, 0.25 to 0.4 mg. daily, without side effects and with improvement in their mental as well as in their circulatory status. It is difficult to decide in advance how a patient will react, but we avoid rauwolfia alkaloids in patients at a time of emotional crisis or when there is a history of mental breakdown. The use as a preliminary measure of 0.25 mg. of reserpine daily in addition to hydrochlorothiazide is a suitable background therapy in a majority of patients, and in a proportion of mild cases will be sufficient to reduce the blood pressure adequately. There is usually no objection to the drugs being combined in one tablet. We found that 23 per cent of our patients could be controlled on background therapy alone,[25] but most of them were among the milder cases coming to us.

Use of gravity-augmented hypotensive drugs. There are now several chemical groupings of the drugs which, by interfering with the action of the sympathetic nervous system, prevent those homeostatic adjustments of the circulation which, in hypertension, are maintaining the level of the blood pressure at an abnormally high level. It should be recognized that postural hypotension is not a side effect of these drugs but is an inevitable consequence of interfering with homeostasis. In the case of the ganglion-blocking drugs, one may make the generalization that practically all stimuli which, homeostatically, call for increased activity of the sympathetic system lead to an increase of the hypotensive action of these drugs. Probably this statement applies to all the gravity-augmented hypotensive drugs because, under such conditions, the level of the blood pressure is more dependent on sympathetic vasoconstriction. Conversely, stimuli which call for a decrease in the homeostatic discharge of sympathetic impulses lead to a decrease in the response to gravity-augmented hypotensive drugs, because then the level of the blood pressure is less dependent on sympathetic vasoconstriction.

There are many examples of the enhancement of the response to gravity-augmented hypotensive drugs by procedures which are likely to call for increased homeostatic action by the sympathetic nervous system. The effect of the gravity-augmented hypotensive drugs is greatest when the patient is standing, of intermediate degree when he is sitting, and least when he is lying down. The reason is that assumption of the vertical posture is compensated for homeostatically by an increased sympathetic discharge. Restall and Smirk[26] found that application of suction to the body surface has the same effect on the action of hexamethonium as does the vertical posture, and for the same reason. Venesection was shown by Freis and associates[27] and O'Donnell[28,29] to enhance the response to hexamethonium. Venous congestion of both lower limbs has the same effect. The explanation is that bleeding or the pooling of blood in veins calls for

compensatory increase of the activity of the sympathetic nervous system; hence, there are more impulses to be removed by hypotensive drugs which act upon the homeostatic mechanisms. Salt restriction was shown by Restall and Smirk[30] and Freis[27] to increase the circulatory response to hexamethonium, and this has been further confirmed by O'Donnell.[29] A decrease of plasma volume often occurs in patients deprived of salt, and it seems likely that deprivation of salt leads to a homeostatic increase of the sympathetic activity. The effect is not due solely to the depletion of sodium, for O'Donnell[29] showed that restoration of the blood volume in salt-depleted patients by infusion of a salt-free dextran solution reduced the postural hypotension induced by hexamethonium, and abolished the enhancement of the action of hexamethonium by the salt deprivation. Exercise, by dilating blood vessels in the voluntary muscles; meals, by causing dilatation in the splanchnic system[13]; purgatives and diuretics, by decreasing either the extracellular fluid volume or the plasma volume,[31] would all appear to call for an increase in homeostatic activity of the sympathetic nervous system in order to prevent a fall of blood pressure, and all may enhance the response to ganglion-blocking drugs.

There are also examples of a decrease of the response to ganglion-blocking drugs which results from the application of procedures which are likely to call for decreased homeostatic action by the sympathetic nervous system. Probably, similar effects would be noted with all the gravity-augmented hypotensive drugs. Examples are: the effect of immersion of the body in water,[32] which acts by counteracting the effect of gravity upon the circulatory system; administration of pressor drugs,[33] such as noradrenaline, angiotensin, s-methylisothiourea; and increase of blood volume by the infusion of blood or dextran solution.[29]

If one of these potent drugs is required in order to reduce the blood pressure, then, to get the best effects with the smallest dose the patient should be standing or sitting during the day, and during the night he should be propped up in bed with a back rest at an angle of 45 degrees. In patients with severe hypertension the reduction of blood pressure during sleep alone is quite insufficient, and also ineffective is the suggestion that the patient use an extra pillow. We instruct our patients in the construction of a simple version of a cardiac bed (Smirk[4]), and the majority of our patients sleep sitting up.

The gravity-augmented hypotensive drugs may be divided into two main classes.

1. Ganglion-blocking drugs. There are three chemical groupings of ganglion-blocking drugs: quaternary ammonium compounds, such as pentolinium; secondary amines, such as mecamylamine; and tertiary amines, such as pempidine M & B 4500 and M & B 5409A. All the ganglion-blocking drugs inhibit the action of both the parasympathetic and the sympathetic nervous systems. Hence, some parasympatholytic side effects must be regarded as a usual association of the use of ganglion-blocking drugs alone. However, if ganglion-blocking drugs are used in combination with other drugs which potentiate the sympatholytic action, the dose administered may fall below the threshold at which parasympatholytic side effects make their appearance. Hexamethonium, the first of these substances to be used in the treatment of hypertension, is now almost superseded, although, on occasion, for an investigation or to produce a prompt but comparatively brief effect, injections of it are employed. Oral hexamethonium is unsatisfactory for most patients because of unpredictable absorption and side effects.

Pentolinium (Ansolysen)[34-36] was the next drug to be used widely, and remains a valuable substance. Over a period of 7 years, extensive-use, long-term toxic effects do not appear to have developed. The substance may show unpredictable absorption but is satisfactory for many patients, even more so since the effective dose can be reduced considerably when a background therapy of a rauwolfia alkaloid and a hypotensive diuretic is employed. As with the use of most of the early quaternary ammonium compounds, drug toleration develops, so that the dose has to be increased gradually for a period of perhaps 2 or even 3 months. Eventually, the dose becomes comparatively stable. A suitable initial single dose is 20 mg., but very large doses, even 500 mg., are required eventually in some patients.

Chlorisondamine (Ecolid) resembles pentolinium closely. Its potency is approximately twice that of pentolinium. Trimethidinium (Ostensin) also resembles pentolinium closely,[37,38] but has the advantage that toleration to it does not occur to any appreciable extent. It is not completely absorbed from the alimentary canal and is a quaternary ammonium compound. Effective action seldom develops with less than 20 mg. (single dose), and doses of over 250 mg. are needed in some patients.

Mecamylamine (Mevasine, Inversine)[39] is a secondary amine, and its principal difference from the quaternary ammonium compounds already mentioned is that it is absorbed completely from the alimentary tract, and there is no appreciable development of drug toleration. If it is given on an empty stomach, its absorption seems to be more predictable than that of any of the quaternary ammonium compounds. Unlike the quaternary ammonium compounds, it has occasionally given rise to instances of long-term toxicity. Gross tremors and severe mental disturbances, sometimes fatal, have occurred. When toxicity is recognized early, the experience of our clinic has been that improvement occurs spontaneously on withdrawal of the drug. The dose of mecamylamine may be as small as 1.25 mg., which is a suitable initial dose, although most patients require more than 2.5 mg., and some require over 30 mg.

Pempidine (Perolysen) is a tertiary amine which, like mecamylamine, is completely absorbed from the alimentary canal. The action is more predictable than that of the quaternary ammonium compounds. Pempidine and its homologues, M & B 4500 and M & B 5409A, are at the present time the most potent of the ganglion-blocking drugs.[40] They appear to be completely absorbed from the alimentary canal and do not lead to the development of drug toleration. No long-term toxicity has emerged from their use. Pempidine is available in 1, 5, and 10-mg. tablets. The initial dose of pempidine should be 1 or 2.5 mg., which may be administered before breakfast, at 2 P.M., and at bedtime. If the patient is well enough, the blood pressure should be taken while he is standing, since this will reveal the maximum extent of the fall of blood pressure. Attempts to bring the blood pressure down while the patient is lying down merely involves the use of much larger doses of ganglion-blocking drugs, with a corresponding increase of the side effects.

The dose may be raised rapidly. Our usual practice when blood pressures are being observed hourly or more frequently by trained technicians is to administer 2.5 mg. of pempidine initially, and a further 1 mg. every hour and a quarter until the blood pressure has fallen to a perceptible degree, and then to continue administering the drug, but at less frequent intervals, until an effective dose has been discovered. In our experience, the final dose attained has averaged 8.3 mg., and occasionally has been as high as 18 mg., but sometimes a dose of 2.5 mg. has been excessive, and 1 mg. two or three times daily has proved sufficient with background therapy. If M & B 4500 is used, the doses are approximately half those of pempidine, whereas with M & B 5409A the dose is approximately 10 per cent higher than the dose of pempidine.

All of the ganglion-blocking drugs can be used in virtually the same way, provided that they do not give rise to drug toleration. Mecamylamine (2.5 and 10-mg. tablets) may be used as an alternative to pempidine, with 1.25 mg. as an initial dose, to be repeated at intervals of about one and a quarter hours until an effective dose has been discovered. The final dose varies greatly from patient to patient but is usually under 30 mg. and rarely as high as 70 mg. When patients are on background drugs, the dosage range for mecamylamine is lower.

The sympatholytic drugs. Sympatholytic drugs without parasympatholytic effects, of recent origin are: bretylium tosylate (Darenthin), a quaternary ammonium compound; and guanethidine (Ismelin), an amidine. Some obscurities remain as to their exact modes of action, but it is generally agreed that they affect the postganglionic part of the sympathetic nervous system in particular and probably have something to do with the release of noradrenaline at sympathetic nerve endings. In most patients, either of these drugs in adequate dosage will reduce the blood pressure.

BRETYLIUM TOSYLATE (DARENTHIN). Although having a different site of action,

bretylium tosylate may be treated as if it were a ganglion-blocking drug, but without an effect upon the parasympathetic nervous system.[41-43] It has the same order of duration of action as pempidine, varying in individual patients from 3 to 12 hours; larger doses produce a longer action.

Bretylium tosylate is not a highly potent drug, and the large doses which have to be given when the drug is employed by itself may give rise to irregular action, presumably because of irregular absorption. We have encountered episodes of unexpectedly large variations of response in patients on large doses. Although overactivity of the parasympathetic nervous system, due presumably to some lack of balance resulting from depression of the sympathetic nervous system, does not make itself evident in a majority of cases, yet in some patients, symptoms such as diarrhea and the exacerbation of dyspepsias suggest the occurrence of parasympathetic overactivity or preponderance. Perhaps the large dose has something to do with the occurrence of indigestion.

The effective single dose of bretylium tosylate will rarely be as low as 100 mg., and may, on occasion, exceed 600 mg. A single, fully effective morning dose which reduces the trough blood pressure of the standing patient to about 130/85 mm. Hg may cause a 12-hour reduction of blood pressure. Usually, we find that an additional, somewhat smaller dose at about 2 P.M. is necessary for adequate control of the blood pressure.

GUANETHIDINE (ISMELIN). This drug has a much longer duration of action than does bretylium tosylate.[43] Once the blood pressure has been brought down to a satisfactory level, the return of the blood pressure to the original height after withdrawal of the drug may take 2 or even more days. Hence, with guanethidine, care is needed to avoid cumulative effects. A dose which may have little effect on the blood pressure on the first or second day may have an excessive action when continued. We have preferred, therefore, to initiate guanethidine therapy gradually and have so far regarded it as less suitable than ganglion-blocking drugs for starting treatment in severe cases. The long duration of action has caused some apprehension lest a patient who might develop a cardiac infarction should be embarrassed by the long-continued action of the drug. In several patients, therefore, I have used guanethidine in combination with background therapy and a small dose of a ganglion-blocking drug, so that in the event that discontinuance of hypotensive therapy became desirable, a prompt decrease in the hypotensive action could be obtained by withdrawal of treatment.

The administration of guanethidine has been associated on occasion with such side effects as muscle pains, sensations of nervous tension, nausea, malaise, nasal obstruction, and failure of ejaculation, as a rule without impotence. Background therapy, when used in combination with guanethidine, may serve to eliminate any side effects which occur when the drug is given by itself. Effective daily doses of guanethidine are usually less than 100 mg. in divided doses, and sometimes as low as 30 mg. Even 180 mg. daily may have no obvious effect on the blood pressure in the first few days, but with accumulation may cause hypotension.

Treatment by combination of drugs

Our general impression is that at the present time the best results are to be obtained by the use of suitable combinations of hypotensive agents. In cases of milder hypertension, the Grade-II type of patients in whom there is no immediate urgency, our recommendation would be to start with background therapy, using 50 mg. of hydrochlorothiazide at bedtime and breakfast time, with 0.75 Gm. of potassium chloride twice daily and 0.125 or even 0.25 mg. of reserpine twice daily. If the blood pressure is not unduly high, it is practicable to wait 2 or 3 weeks for the action of the reserpine to become fully established. If however, the patient has a very high blood pressure, for example, a casual blood pressure of 230/130 mm. Hg or higher, it is usually desirable to add bretylium tosylate or guanethidine in gradually ascending doses. If the patient can be observed continuously throughout the day, our practice is to administer 100 mg. of bretylium tosylate at intervals of approximately 1½ hours until such time as the blood pressure begins to fall. This enables

one to judge the magnitude of an effective dose. The lowest dose we have used, combined with background therapy, is about 50 mg. thrice daily: before breakfast, at 2 P.M., and at bedtime. The highest dose of bretylium tosylate which we have used continuously is 600 mg. thrice daily. As a rule, however, if the requisite dose of bretylium tosylate has exceeded 300 mg., we have preferred to add small doses of one of the more potent ganglion-blocking drugs, for example, pempidine, rather than increase further the dose of bretylium tosylate.

With a choice of many drugs which differ in their properties and have value in particular situations, the range of useful regimens cannot be briefly summarized. Among the ganglion-blocking drugs, my first choice for administration to a previously untreated patient would be pempidine or one of its homologues, M & B 4500 or M & B 5409A.[40] Mecamylamine, on occasion, has given rise to gross tremors and to mental disturbance, with an occasional fatality, whereas the pempidine group of drugs does not appear to show delayed toxicity. If, however, a patient is already well controlled with some drug, such as pentolinium, trimethidinium, or chlorisondamine, it will not need to be discontinued; but with these there is the disadvantage of drug toleration, which, when therapy is initiated, will delay the establishment of a stable regimen. Patients who are on background therapy but who require the addition of a more potent substance will often remain comfortable when a ganglion-blocking drug is added to the regimen. Alternatively, one may add bretylium tosylate or guanethidine, or a judicious combination of one of these with a ganglion-blocking drug. By the selection of appropriate doses it is almost always practicable to avoid significant parasympathetic and parasympatholytic side effects.

It has been shown by Smirk[44] that with a satisfactory spacing of the drugs now available it usually happens that if the blood pressure at the trough of the blood-pressure fall is reduced to, or near to, a fully normal level of 120/80 mm. Hg, the blood pressure during the rest of the day is likely to be satisfactory. It was shown that the blood pressure at the trough of the blood-pressure fall is closely related to the average pressure throughout the day.

Whenever all-day tests are impracticable, the patient may be instructed to raise suitably spaced doses of the more potent hypotensive agents by small increments until such time as a slight faintness results at the trough of the blood-pressure fall. The increments should be added at intervals of 1 or 2 days. If, then, the last small increment which gave rise to mild hypotension is removed, the probability is that an important degree of control of the blood pressure has been attained. Details of the method of establishing control by various ganglion-blocking drugs has been published elsewhere.[4] This method is applicable without modification to bretylium tosylate. In the case of guanethidine, however, adjustments in dosage must be gradual, and a week or more may elapse before the full effect of a change in dosage can be evaluated.

In severe cases, especially in patients with Grade IV retinal changes, troubles such as ileus are more likely to occur at an early stage if ganglion-blocking drugs are used alone. To avoid this serious complication we give background therapy and replace some of the ganglion-blocking drug with bretylium tosylate. Approximately equivalent doses are 4 mg. of pempidine equals 2 mg. of M & B 4500 equals 85 mg. of bretylium tosylate. Ileus or a threat of ileus seems to have been much less frequent since this practice was adopted.

Summary

1. At the present time, very few patients should suffer persistent discomfort from the use of effective hypotensive therapy.

2. Although the hypotensive diuretics alone, or even in combination with rauwolfia alkaloids, will not always suffice to reduce the blood pressure much more than does a placebo, there is in almost every case a distinct enhancement of the response to ganglion-blocking drugs and to the new sympatholytic drugs, bretylium tosylate and guanethidine. This action has a distinct advantage, for it makes possible a background form of therapy upon which comparatively small doses of ganglion-blocking or sympatholytic drugs may suffice, even in severe cases.

3. For severe cases the most generally satisfactory approach is not by one of the sympatholytic drugs and background therapy alone but by the introduction additionally of a small dose of a ganglion-blocking drug into the regimen in order to preserve a satisfactory balance between the activities of the sympathetic and parasympathetic nervous systems. Even without background therapy it is usually possible to combine bretylium tosylate or guanethidine with a potent ganglion-blocker in doses which give rise to no significant side effects from either group of drugs. Background therapy is, however, desirable to obtain a more stable regimen. If a sympatholytic drug is to be combined with a ganglion-blocking drug, it is preferable to use a ganglion-blocking drug to which there is not significant toleration. Mecamylamine, and pempidine with its potent homologues M & B 4500 and M & B 5409A, are examples. In patients who have had a peptic ulcer it seems unwise to use sympatholytic drugs without employing ganglion-blocking drugs to restrain gastric secretion.

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Annotations

The blight of medical science

Allan Gregg once said, "The medical literature of today exemplifies all too fully the biological adage that life is choked by its own secretions."[1] It is clear that the ever-increasing volume of scientific medical production in this country, primed, fostered, forced, and bought by millions of dollars lavished on institutions and individuals carries within itself the lethal seed of oblivion. To be of permanent value, research needs to record, publish, and publicize its results. Yet the tidal wave of overproduction in the biological sciences has made it almost impossible (a) to provide a forum for early presentation in the conventional framework of scientific journals, and (b) for the individual investigator to know and assess the activities of others even in his own limited field. In an address before the Southern Society for Clinical Research, A. Segaloff[2] has raised this problem. According to Segaloff, today 25,000 journals are devoted to the biological sciences, containing in a single year some two million articles on biology. It is interesting that this appalling state seemed to have alarmed very few scientists, yet obviously it is of immediate and worldwide concern. Some time ago, during a "Symposium on Utilization of Recorded Knowledge,"[3] G. M. Conrad demonstrated the nearly parabolic curve of journal growth in the field of biology, which showed that even present methods of abstracting will become totally inadequate during the present decade. This means that the more investigations have been completed, the less the likelihood that anyone will know about it. Into this climate comes the estimate of the Bayne-Jones report on "The Advancement of Medical Research and Education."[4] The report, a plea for more and better medical training areas, states that 20,000 new medical scientists (conservatively, 40,000 additional "papers" per year) will be added to the load by 1970, in this country alone. A more recent analysis[5] stresses the need for the immediate creation of at least 20 new medical schools in this country. If this is realized, and if present standards prevail, a sharp increase in the output of medical research far beyond the present anticipated increase in volume can be predicted. Private abstracting services, the always incomplete abstract sections of some journals, Biologic Abstracts in the U.S. (36,000 per year), Chemical Abstracts, or similar services in the U.S.S.R. (106,000 articles per year) are already inadequate. Mere indexing alone does not suffice. Segaloff suggests that most journals should only publish abstracts prepared by the author himself, who would also be required to code his results according to a universal system. A central institute could microfilm and distribute the original manuscript on request. The machine code, identical for any language, would thus become the universal language of science.

This seems radical but it is likely that publication of full articles other than reviews will become an anachronism whether we like it or not. Few of us read a journal, or even an article, from beginning to end, but rely on carefully written "introductions" (to discover the problem) and "summaries" (to know what was done and what was accomplished). "Federation" abstracts, for example, abstracts of the annual meetings of the Society for Clinical Investigation (June issues of *Journal of Clinical Investigation*), and similar services ("Clinical Research" and others) are often sufficiently detailed as a first approximation even for those working in the field. It might be argued: Why waste excessive printing cost and time if the essential information can be obtained from carefully written abstracts? If such a radical departure in methods of communication in science becomes necessary, and it seems that something must "give" soon, several copies of a full manuscript, tables, and illustrations intended for publication in a national journal should be submitted to the editor and his editorial board for review before even an abstract of the manuscript is accepted for publication. Reprints of the abstract must be made available. The full text of the communication should be deposited in several regional centers, where the article could be studied in the original or where a competent staff could supply microfilm copies and translations on demand. The libraries of major medical centers may serve as a nucleus for such information centers. The considerable expenses involved must in a large measure be charged to research, and agencies granting funds for research must then include in their appropriations large sums for financial support of a communication system of some sort, a suggestion recently made by Milton Lee and incorporated in the report mentioned above.[5] Thus, two kinds of journals can be visualized: the abstract journal, which is primarily directed to the medical research worker, and the review journal, such as *Medicine*, or *Physiologic Reviews*, which are designed exclusively as projects in postgraduate education. To be truly effective, such changes would require the cooperation of all national biological groups, editors of "clinical" and "preclinical" journals, library associations, and national health agencies. It needs international acceptance as well, possibly through the UNESCO and the World Health Organization.

Although the medical scientist, and the ultimate "consumer," the practicing physician, are only dimly aware of the problem, strong efforts are being made to stem the tide before it becomes unmanageable. An increasing number of medical information centers have been created in this country, such as the National Library of Medicine, The National Science Foundation, The National Academy of Science, and others, which provide such services as part of their activities. In specific areas, there exists a cardiovascular research project (NHI), a cancer chemotherapy information center (NIH), and a psychopharmacology service information center. The over-all training and developmental research in the area of scientific communication is planned and carried out by a newly founded "Institute for Advancement of Medical Communication."[7] As an experimental example this Institute assisted in UNIVAC programming of the 1960 meetings of the Federated Societies of Biology and Medicine. An International Conference on Scientific Information was held in Washington in 1958, and has issued its voluminous Proceedings,[8] by itself perhaps proof of the inadequacy of our present communication system. A Conference of Biologic Editors (CBE) has been formed whose committees are concerned with many of the pressing facts of medical communication. In consultation with other groups, such as the American Medical Writers Association, CBE is about to publish a "Style Manual" as a first step toward unifying certain obvious aspects of medical writing and editing practices.[9]

We are likely to see significant changes in medical communication in our time. Medical scientists and clinical investigators will have to recognize their responsibilities in this respect. Little can be accomplished, however, if a well-written abstract "does not count," if the practice of a forced completed manuscript is tied to an oral presentation before a clinical society, or if scientific groups and universities continue to gauge an investigator's qualification by the number rather than the substance of his publications. This fosters quantitative mediocrity, one of the major contributors to the blight of medical science.

Hans H. Hecht, M.D.
Salt Lake City, Utah

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Bruit de Roger

If a harsh murmur with or without an accompanying thrill is found to be most intense just to the left of the sternum in the third or fourth intercostal space, the differential diagnosis revolves about interventricular septal defect and isolated pulmonic stenosis. The latter condition was less well defined in Roger's time. In favor of septal defect is left as well as right ventricular enlargement as determined by x-ray examination or fluoroscopy as well as by electrocardiography. Bundle branch block is helpful if present, and prominent pulmonary vascular markings with or without hilar pulsations are characteristic. In pulmonic stenosis there is right ventricular enlargement only and the vascular markings are less well defined, although poststenotic dilatation may produce a prominent left hilar shadow. Transmission of the murmur to the right in septal defect and upward and to the left in pulmonic stenosis is rarely of much help in differentiating the two conditions clinically.

Interauricular septal defect can sometimes be confusing here, since the lesion may produce a murmur in the same region, although an associated thrill is uncommon. The murmur is believed to arise in the pulmonary artery because of the turbulence caused by increased pulmonary blood flow. The prominence of the pulmonary artery in both hila as well as the hilar dance are usually distinguishing features, but differentiation from interventricular septal defect is not always possible. Today these clinical surmises can be confirmed or denied by the catheter and in the operating room.

Milton Mendlowitz, M.D.
New York, N.Y.

Concept of a dual circulation

In recent years the argument that some of the blood flowing through the skin is *not* involved in the nourishment of the tissue has become universally accepted. Arteriovenous shunts have been demonstrated histologically, and much information has been gathered about their regulation and their role in the control of the temperature of the body.[1] Analogous shunts in skeletal muscle are vigorously denied, since only a few morphologic demonstrations of such vessels have been reported,[2] and almost all of the evidence for shunts in muscle is inferential. The weight of these circumstantial demonstrations, however, is increased by their consistency and the number of experiments which cannot be easily explained in any alternative fashion.[3]

One difficulty in accepting the concept of vascular shunts in muscle has to do with assigning to them a valid physiologic role. Although the movement of a large volume of blood through the skin serves to regulate the temperature of the body,[4] movement of blood through skeletal muscle can have no similar effect. The participation of an increase in the flow of blood through muscle in regulation of the blood pressure is hardly more likely, since many alternative tissues are available through which compensatory increases in the flow of blood can easily be achieved.[5] As a third alternative, we suggest that the blood flowing through the shunts brings to the muscle a quantity of heat which causes an increase in temperature that might increase efficiency of contraction. Although the amount of heat which could be carried by such a system would be small in comparison to that locally produced during contraction of the muscle, such a mechanism could prepare for the initial response.

It is interesting to note that the shunt circulation in this tissue is undoubtedly under central nervous control: vasodilator fibers have been demonstrated to be supplying muscles in animal preparations in which these phenomena have been studied.[6] These fibers, arising in the central nervous system, may be associated with the motor outflow to skeletal muscle, and thus might serve to increase the flow of blood in those specific muscles which are soon to be activated.

Such a shunt circulation would have interesting clinical implications. It would help to explain those paradoxical situations in which the total flow of blood through a muscle is increased yet the underlying pathologic complaint, viz., claudication or inadequate tissue nutrition, still persists.[7] Obviously, agents or mechanisms which open the shunt circulation without modifying nutritional supply would contribute to an increased total flow of blood but would in no way increase the turnover of tissue solutes and, hence, would not obviate the basic malnutrition of this tissue.[8]

Much work remains to be done on this problem since the existence of a shunt circulation in the muscles of human beings has not yet been clearly demonstrated, and since actual control of these vessels is uncertain in all but a very few species. The explanation or, rather rationalization, for the function of such bypass systems is highly conjectural and awaits further experimental study.

Chester Hyman, Ph.D.
Los Angeles, Calif.

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Cardiac glycosides and the kidney

Withering was certainly aware of the cardiac action of digitalis, but attributed the clinical improvement that followed its administration to patients with dropsy to an increased excretion of urine as a result of a primary, direct effect on the kidneys. Subsequently, many clinical and experimental observations in patients with congestive heart failure have established that the cardiac glycosides initially effect

an improvement in myocardial function and circulatory dynamics. With this in mind, it was held that the observed diuresis was related to the accompanying increase in glomerular filtration rate and renal blood flow. This concept was supported by the observations of Bartram,[1] who was unable to show a clear-cut ipsilateral diuresis in response to the intrarenal arterial injection of Digitan. In contrast, Farber and associates[2] noted that in a few edematous subjects the intravenous administration of digoxin was followed by a slight diuresis and natriuresis, without any prior or accompanying hemodynamic changes. Following the observations by Schatzmann[3] on the influence of the cardiac glycosides on the rate of transport of sodium and potassium across the membrane of the human erythrocyte, a number of investigators have shown that these agents induce alteration in the bidirectional flux of several ions across the membranes of many other cells.

A direct renal response evoked by cardiac glycosides or aglycones has been confirmed by recent reports from several laboratories,[4-6] including our own,[7] in which simultaneously comparative analyses of the function of both kidneys have been made after the slow unilateral renal arterial injection of these agents. In our experimental preparations, the effects include a striking increase in the rate of flow of urine from the ipsilateral kidney, amounting to 3 to 4 times the rate from the contralateral kidney. Along with this diuresis, there is a natriuresis and a chloruresis. Changes in the rate of excretion of potassium are variable and of small degree. A pronounced ipsilateral increase occurs in the excretion of calcium and, to a somewhat lesser extent, of magnesium as well. Both the glomerular filtration rate and renal plasma flow of the ipsilateral kidney decline initially but return toward control levels thereafter.

It appears more and more likely that the primary change in cardiac function which is responsible for the observed beneficial therapeutic effects of the cardiac glycosides in patients with congestive heart failure is induced by the alterations in the rate of movement of ions across the myocardial cell membrane. The observations cited above lead to the conclusion that these drugs also directly affect active renal tubular transport mechanisms for several ions in a manner which promotes diuresis. Much work remains to be done to elucidate further the intriguing effects on the interrelated patterns of excretion of electrolytes and water induced by these drugs, and the manner in which their activity is seemingly enhanced or inhibited by altered distribution of electrolytes.

Sherman Kupfer, M.D.
Jonah D. Kosovsky, M.D.
New York, N.Y.

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Book reviews

THE HEART IN INDUSTRY. Edited by Leon J. Warshaw, M.D., F.A.C.P., Consultant in Occupational Health; Medical Director, Paramount Pictures Corporation; Medical Director, United Artists Corporation, New York. New York, 1960, Paul B. Hoeber, Inc., 677 pages. Price $16.

The Editor's opening chapter, a particularly well-written survey of cardiovascular disease in industry, sets the scene for the chapters which follow. These present, in comprehensive yet understandable form, present-day concepts of the effect of heart disease on the patient and his ability to work, the effects of work on the course of his heart disease, and certain problems presented by the cardiac worker to his employer. Along with the conventional subjects expected in such a volume, there are noteworthy presentations on: the cardiac as a vehicle operator in transportation; the cardiac on the farm (a particularly refreshing sequence from the Purdue Farm Cardiac Project—incidentally, neither author is a physician); cardiovascular effects of toxic occupational exposures (including a discourse on fundamental toxicology); traumatic heart disease (a subject often overlooked by non-surgical practitioners of cardiology); and health education in industry (wherein the approach to the individual receives proper emphasis). Although most topics are well handled, the treatment of workmen's compensation and heart disease misses the mark. As perceived by this reviewer, this chapter attempts a description of the evolution of workmen's compensation doctrine, followed by an apology for the inconsistent, unscientific decisions so prevalent today, with implied criticism of some of the current efforts to achieve a sounder medicolegal operation in this chaotic field.

Considerable repetition of content is present. In fact, one wonders about such consistency in point of view on the part of the different authors in introducing and developing their topics. Does this reflect the guiding hand of the Editor, is it provincialism (the majority of the collaborators are New Yorkers), or does a state of general agreement actually exist about matters relating to work and heart disease? At any rate, the prevailing concepts are both reasonable and constructive.

The format of the book and the relatively uncomplicated presentation of such matter make easy reading. Typographic errors detected by the reviewer were infrequent, especially for a first printing. Numerous tables lend clarity to the material presented. The lists of references at the end of each chapter, although limited, serve to introduce the interested reader to some key publications on each subject.

"Intended for both the industrial physician and the private practitioner," "written by clinicians for clinicians," "emphasizing the practical rather than the theoretical"—these are among the attributes of the book listed by the Editor and publishers. It does, indeed, well fulfill these characteristics, and should be widely read.

HYPERTENSION. VOLUME III: RENAL, ELECTROLYTE AND AUTONOMIC FACTORS (Proceedings of the Council for High Blood Pressure Research, American Heart Association, November, 1959). Edited by Floyd R. Skelton, M.D., Ph.D., Research Director, The Urban Maes Research Foundation, and Associate Professor of Pathology, Louisiana State University School of Medicine, New Orleans, La. New York, 1960, American Heart Association, 150 pages.

This publication represents the Proceedings of the Council for High Blood Pressure Research of the American Heart Association, November, 1959. Six papers are presented. The first paper is by Dr. Louis Tobian on "The Juxtaglomerular Apparatus in Experimental Hypertension," in which considerable circumstantial evidence relating the granularity of juxtaglomerular apparatus of Goormaghtigh to renin secretion is cited. A second paper by E. E. Muirhead presents evidence that the renal medulla may be the critical portion of the kidney which protects against renoprival hypertension. A third paper by O. M. Helmer and W. E. Judson describes the isolation of vasopressor material from the renal vein of some but not all hypertensive subjects as well as of normotensive subjects with congestive heart failure.

In a fourth paper by S. M. Friedman and co-workers, evidence is presented which suggests a relationship between contraction of smooth muscle and the gradient between intracellular and extracellular sodium. A fifth paper by Dr. F. J. Haddy discusses the function of small and large peripheral vessels. The importance of oppositely directed changes in arteriolar and venular resistance are stressed and possible reflex arteriolar constriction secondary to venous hypertension is noted. The final paper by S. J. Sarnoff and co-workers is entitled "The Regulation of Function in the Innervated Heart." In a series of elegantly contrived and painstakingly executed experiments the authors demonstrate that sympathetic and vagal stimulation do not primarily alter distensibility characteristics of the heart muscle but exert their effect on contractility. These observations serve to support Starling's concept that neural and chemical factors can serve to increase or decrease the contractile response of heart muscle to a given stretch.

The various approaches to problems relating to the circulation and hypertension are presented in some detail and amplified and clarified by the group discussions which follow.